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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:

HUNTER et al.

Serial No.: 10/071,751

Filed: February 7, 2002

Atty. File No.: 2618-17-C4-PUS-2

For: "NOVEL ECTOPARASITE SALIVA  
PROTEINS AND APPARATUS TO  
COLLECT SUCH PROTEINS"

Assistant Commissioner for Patents  
Washington, D.C. 20231

RESPONSE TO NOTICE TO FILE  
CORRECTED APPLICATION PAPERS  
AND REQUEST FOR CORRECTION  
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Dear Sir:

In response to the Notice to File Corrected Application Papers, dated March 27, 2002, enclosed is a copy of the substitute specification. The substitute specification is identical in content to the originally filed specification and therefore contains no new matter. The substitute specification is filed merely to correct the improper margin, as required by the Notice.

Please revise the official Filing Receipt to correct the following errors:

1. The residence address for Gek-Kee Sim is Fort Collins, CO;
2. The priority data should indicate that this application is a divisional of 09/171,156, filed **October 9, 1998**.

3. Applicants are not aware that 09/171,156 has issued as of this date; therefore, Applicants question the accuracy of listing 6,368,846 in connection with the priority application.

For your reference, a copy of the Filing Receipt is enclosed, with the corrections indicated in red. Please issue a corrected Filing Receipt for this patent application.

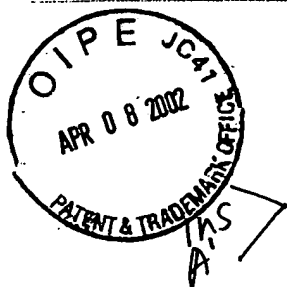
Respectfully submitted,

SHERIDAN ROSS P.C.

By: Angela Dallas

Angela K. Dallas  
Registration No. 42,460  
1560 Broadway, Suite 1200  
Denver, CO 80202-5141  
(303) 863-9700

Date: April 4, 2002



File No. 2618-17-C4-PCT

NOVEL ECTOPARASITE SALIVA PROTEINS  
AND APPARATUS TO COLLECT SUCH PROTEINS

FIELD OF THE INVENTION

The present invention relates to a novel product and method for isolating ectoparasite saliva proteins, and a novel product and method for detecting and/or treating allergic dermatitis in an animal.

BACKGROUND OF THE INVENTION

10 Bites from ectoparasites, in particular fleas, can cause a hypersensitive response in animals. In particular, hypersensitive responses to fleabites is manifested in a disease called flea allergy dermatitis (FAD). Hypersensitivity refers to a state of altered reactivity in  
15 which an animal, having been previously exposed to a compound, exhibits an allergic response to the compound upon subsequent exposures. Hypersensitive responses include immediate and delayed-type hypersensitivity, and in particular Type I, Type II, Type III and Type IV  
20 hypersensitivities (described in detail in Janeway et al., *Immunobiology*, Garland Publishing, New York, 1994, which is incorporated in its entirety by this reference).

Foreign compounds that induce symptoms of immediate and/or delayed hypersensitivity are herein referred to as  
25 allergens. The term "allergen" primarily refers to foreign compounds capable of causing an allergic response. The term can be used interchangeably with the term "antigen,"

especially with respect to a foreign compound capable of inducing symptoms of immediate and/or delayed hypersensitivity. Factors that influence an animal's susceptibility to an allergen can include a genetic component and/or environmental exposure to an allergen. Animals can be de-sensitized to an allergen by repeated injections of the allergen to which an animal is hypersensitive.

FAD can have manifestations of both immediate and delayed-type hypersensitivity (described in detail in Janeway et al., *ibid.*). Effective treatment of FAD has been difficult if not impossible to achieve. FAD afflicts about 15% of cats and dogs in flea endemic areas and the frequency is increasing each year. In a geographical area, effective flea control requires treatment of all animals. One treatment investigators have proposed includes desensitization of animals using flea allergens. However, reliable, defined preparations of flea allergens are needed for such treatments.

Until the discovery of the novel formulations of the present invention, flea allergens responsible for FAD had not been clearly defined. Whole flea antigen preparations have been used to diagnose and desensitize animals with FAD (Benjamini et al., 1960, pp. 214-222, *Experimental Parasitology*, Vol. 10; Keep et al., 1967, pp. 425-426,



Australian Veterinary Journal, Vol. 43; Kristensen et al., 1978, pp. 414-423, Nord. Vet-Med, Vol. 30; Van Winkle, 1981, pp. 343-354, J. Amer. Animal Hosp. Assoc., Vol. 17; Haliwell et al., 1987, pp. 203-213, Veterinary Immunology and Immunopathology, Vol. 15; Greene et al., 1993, pp. 69-74, Parasite Immunology, Vol. 15); PCT Publication No. WO 93/18788 by Opdebeeck et al.; and Van Winkle, pp. 343-354, 1981, J. Am. Anim. Hosp. Assoc., vol. 32. Available commercial whole flea extracts, however, are unpredictable and, therefore, have limited usefulness.

Prior investigators have suggested that products contained in flea saliva might be involved in FAD and have also suggested methods to isolate such products: Benjamini et al., 1963, pp. 143-154, Experimental Parasitology, Vol. 13; Young et al., 1963, pp. 155-166, Experimental Parasitology 13, Vol. 13; Michaeli et al., 1965, pp. 162-170, J. Immunol., Vol. 95; and Michaeli et al., 1996, pp. 402-406, J. Immunol., Vol. 97. These investigators, however, have characterized the allergenic factors of flea saliva as being haptens having molecular weights of less than 6 kilodaltons (kD). That they are not proteins is also supported by the finding that they are not susceptible to degradation when exposed to strong acids (e.g., 6 N hydrochloric acid) or heat. Some of the particular low molecular weight allergenic factors have also been

characterized as being a highly fluorescent aromatic fraction (Young et al., *ibid.*). In addition, studies by such investigators have indicated that in order to be allergenic, such factors need to be associated with adjuvants and/or carriers, such as collagen or portions of the membrane used to collect the oral secretions. Moreover, the methods described to collect flea saliva factors were difficult and unpredictable. Furthermore the factors isolated by these methods were typically contaminated with material from the fleas, their culture medium or the skin-based membranes used to allow the fleas to feed.

Thus, there remains a need to more clearly define flea saliva allergens capable of inducing a hypersensitive response in animals. In addition, there remains a need to develop a method to collect substantially pure flea saliva allergens which provide predictable and less expensive preparations of allergens useful for desensitizing animals subject to, or having, FAD.

#### SUMMARY OF THE INVENTION

One embodiment of the present invention is an isolated nucleic acid molecule that hybridizes under stringent conditions with a gene including a flea saliva gene comprising a nucleic acid sequence including SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID

NO:73, SEQ ID NO:74, SEQ ID NO:76 and a nucleic acid sequence encoding an amino acid sequence selected from the group consisting of SEQ ID NO:78 and SEQ ID NO:87.

5 The present invention also includes a nucleic acid molecule that hybridizes under stringent hybridization conditions with a nucleic acid molecule having a nucleic acid sequence encoding a protein comprising an amino acid sequence including SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87.

10 Another embodiment of the present invention includes an isolated protein encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions with a nucleic acid molecule having a nucleic acid sequence encoding a protein comprising an amino acid sequence including SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87.

15 Also included in the present invention are recombinant molecules and cells having a nucleic acid molecule of the present invention.

20 Another aspect of the present invention includes an antibody capable of selectively binding to an ectoparasite protein, or mimetope.

25 Yet another embodiment of the present invention is a therapeutic composition for treating allergic dermatitis

comprising a formulation comprising at least one isolated ectoparasite saliva protein, wherein said ectoparasite saliva protein comprises at least a portion of an amino acid sequence, wherein said portion is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions with a nucleic acid molecule having a nucleic acid sequence including SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76 and a nucleic acid sequence encoding an amino acid sequence selected from the group consisting of SEQ ID NO:78 and SEQ ID NO:87. A preferred therapeutic composition of the present invention also includes an excipient, an adjuvant and/or a carrier. Also included in the present invention is a method to desensitize a host animal to allergic dermatitis. The method includes the step of administering to the animal a therapeutic composition of the present invention.

Other embodiments of the present invention include methods to identify an animal susceptible to or having allergic dermatitis, using *in vivo* or *in vitro* methods. In one embodiment, an animal susceptible to or having allergic dermatitis is identified *in vivo* by the method comprising:

(a) administering to a site on the animal a formulation

comprising at least one isolated ectoparasite saliva protein, in which the ectoparasite saliva protein comprises an amino acid sequence including SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87; and (b) comparing a reaction resulting from administration of the formulation with a reaction resulting from administration of a control solution, in which the animal is determined to be susceptible to or to have allergic dermatitis if the reaction to the formulation is at least as large as said reaction to the positive control solution, and in which the animal is determined not to be susceptible to or not to have allergic dermatitis if the reaction to the formulation is about the same size as said reaction to the negative control solution.

In another embodiment, an animal susceptible to or having allergic dermatitis is identified *in vitro* by measuring the presence of antibodies indicative of allergic dermatitis in the animal using the method comprising: (a) contacting a formulation with a body fluid from an animal under conditions sufficient for formation of an immunocomplex between the formulation and the antibodies, if present, in the body fluid, the formulation comprising at least one isolated ectoparasite saliva protein, in which the ectoparasite saliva protein comprises an amino acid sequence including SEQ ID NO:53, SEQ ID NO:62, SEQ ID

NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87; and (b) determining the amount of immunocomplex formed, in which formation of the immunocomplex indicates that the animal is susceptible to or has allergic dermatitis.

The present invention further relates to an assay kit for testing if an animal is susceptible to or has allergic dermatitis, the kit comprising: (a) a formulation comprising at least one isolated ectoparasite saliva protein, in which the ectoparasite saliva protein comprises an amino acid sequence including SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87; and (b) a means for determining if the animal is susceptible to or has allergic dermatitis, in which the means comprises use of the formulation to identify animals susceptible to or having allergic dermatitis.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention includes a novel product and method for diagnosing and treating allergic dermatitis of animals to ectoparasites.

According to the present invention, ectoparasites are external living parasites that attach and feed through the skin of a host animal. Ectoparasites include parasites that live on a host animal and parasites that attach

temporarily to an animal in order to feed. Also, according to the present invention, ectoparasite saliva refers to the material released from the mouth of an ectoparasite when the ectoparasite attempts to feed in response to a temperature differential. Ectoparasite saliva includes ectoparasite saliva products.

One embodiment of the present invention is a formulation that contains ectoparasite saliva products that can be used to diagnose and/or treat animals susceptible to or having (i.e., suffering from) allergic dermatitis. Preferred types of allergic dermatitis to diagnose and/or treat using ectoparasite saliva products of the present invention include flea allergy dermatitis, *Culicoides* allergy dermatitis and mosquito allergy dermatitis. A preferred type of allergic dermatitis to diagnose and/or treat using ectoparasite saliva products of the present invention is flea allergy dermatitis. As used herein, an animal that is susceptible to allergic dermatitis refers to an animal that is genetically pre-disposed to developing allergic dermatitis and/or to an animal that has been primed with an antigen in such a manner that re-exposure to the antigen results in symptoms of allergy that can be perceived by, for example, observing the animal or measuring antibody production by the animal to the antigen. As such, animals susceptible to allergic dermatitis can include animals having sub-clinical allergic dermatitis.

Sub-clinical allergic dermatitis refers to a condition in which allergy symptoms cannot be detected by simply observing an animal (i.e., manifestation of the disease can include the presence of anti-ectoparasite saliva protein antibodies within an affected animal but no dermatitis). For example, sub-clinical allergic dermatitis can be detected using *in vivo* or *in vitro* assays of the present invention, as described in detail below. Reference to animals having allergic dermatitis includes animals that do display allergy symptoms that can be detected by simply observing an animal and/or by using *in vivo* or *in vitro* assays of the present invention, as described in detail below.

One embodiment of the present invention is a formulation that includes one or more isolated ectoparasite saliva proteins. According to the present invention, an isolated protein is a protein that has been removed from its natural milieu. An isolated ectoparasite saliva protein can, for example, be obtained from its natural source, be produced using recombinant DNA technology, or be synthesized chemically. As used herein, an isolated ectoparasite saliva protein can be a full-length ectoparasite saliva protein or any homologue of such a protein, such as an ectoparasite saliva protein in which amino acids have been deleted (e.g., a truncated version of



the protein, such as a peptide), inserted, inverted, substituted and/or derivatized (e.g., by glycosylation, phosphorylation, acetylation, myristylation, prenylation, palmitation, amidation and/or addition of glycosylphosphatidyl inositol). A homologue of an ectoparasite saliva protein is a protein having an amino acid sequence that is sufficiently similar to a natural ectoparasite saliva protein amino acid sequence that a nucleic acid sequence encoding the homologue is capable of hybridizing under stringent conditions to (i.e., with) a nucleic acid molecule encoding the natural ectoparasite saliva protein (i.e., the complement of a nucleic acid sequence encoding the natural ectoparasite saliva protein amino acid sequence). A nucleic acid sequence complement of any nucleic acid sequence of the present invention refers to the nucleic acid sequence of the nucleic acid strand that is complementary to (i.e., can form a complete double helix with) the strand for which the sequence is cited. It is to be noted that a double-stranded nucleic acid molecule of the present invention for which a nucleic acid sequence has been determined for one strand that represented by a SEQ ID NO also comprises a complementary strand having a sequence that is a complement of that SEQ ID NO. As such, nucleic acid molecules of the present invention, which can be either double-stranded or single-stranded, include those nucleic acid molecules that form

stable hybrids under stringent hybridization conditions with either a given SEQ ID NO denoted herein and/or with the complement of that SEQ ID NO, which may or may not be denoted herein. Methods to deduce a complementary sequence are known to those skilled in the art.

As used herein, stringent hybridization conditions refer to standard hybridization conditions under which nucleic acid molecules, including oligonucleotides, are used to identify similar nucleic acid molecules. Such standard conditions are disclosed, for example, in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press, 1989; Sambrook et al., *ibid.*, is incorporated by reference herein in its entirety. Stringent hybridization conditions typically permit isolation of nucleic acid molecules having at least about 70% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction. Formulae to calculate the appropriate hybridization and wash conditions to achieve hybridization permitting 30% or less mismatch of nucleotides are disclosed, for example, in Meinkoth et al., 1984, *Anal. Biochem.* 138, 267-284; Meinkoth et al., *ibid.*, is incorporated by reference herein in its entirety.

The minimal size of a protein homologue of the present invention is a size sufficient to be encoded by a nucleic

acid molecule capable of forming a stable hybrid with the complementary sequence of a nucleic acid molecule encoding the corresponding natural protein. As such, the size of the nucleic acid molecule encoding such a protein homologue is dependent on nucleic acid composition and percent homology between the nucleic acid molecule and complementary sequence as well as upon hybridization conditions per se (e.g., temperature, salt concentration, and formamide concentration). The minimal size of such nucleic acid molecules is typically at least about 12 to about 15 nucleotides in length if the nucleic acid molecules are GC-rich and at least about 15 to about 17 bases in length if they are AT-rich. As such, the minimal size of a nucleic acid molecule used to encode an ectoparasite saliva protein homologue of the present invention is from about 12 to about 18 nucleotides in length. There is no limit, other than a practical limit, on the maximal size of such a nucleic acid molecule in that the nucleic acid molecule can include a portion of a gene, an entire gene, or multiple genes, or portions thereof. Similarly, the minimal size of an ectoparasite saliva protein homologue of the present invention is from about 4 to about 6 amino acids in length, with preferred sizes depending on whether a full-length, multivalent (i.e., fusion protein having more than one domain each of which

has a function), or functional portions of such proteins are desired.

Ectoparasite saliva protein homologues can be the result of allelic variation of a natural gene encoding an ectoparasite saliva protein. A natural gene refers to the form of the gene found most often in nature. Ectoparasite saliva protein homologues can be produced using techniques known in the art including, but not limited to, direct modifications to a gene encoding a protein using, for example, classic or recombinant DNA techniques to effect random or targeted mutagenesis.

Preferred ectoparasite saliva proteins of the present invention, including homologues thereof, are capable of detecting and/or treating allergic dermatitis resulting from the bites of ectoparasites. A preferred ectoparasite saliva protein homologue includes at least one epitope capable of eliciting a hypersensitive response to the natural ectoparasite saliva protein counterpart. An ectoparasite saliva protein homologue can also include an epitope capable of hyposensitizing an animal to the natural form of the protein. The ability of an ectoparasite saliva protein homologue to detect and/or treat (i.e., immunomodulate or regulate by, for example, desensitizing) the hypersensitivity of an animal susceptible to or having allergic dermatitis, can be tested using techniques known to those skilled in the art. Such techniques include skin

tests and immunoabsorbent assays as described in detail below. Additional preferred ectoparasite saliva proteins of the present invention have other activities that include activities important for feeding and survival of the ectoparasite.

In one embodiment, a formulation of the present invention can comprise a protein having at least a portion of an isolated ectoparasite saliva protein. According to the present invention, "at least a portion of an ectoparasite saliva protein" refers to a portion of an ectoparasite saliva protein encoded by a nucleic acid molecule that is capable of hybridizing, under stringent conditions, with a nucleic acid encoding a full-length ectoparasite saliva protein of the present invention. Preferred portions of ectoparasite saliva proteins are useful for detecting and/or treating allergic dermatitis resulting from the bites of ectoparasites. Additional preferred portions have activities important for flea feeding and survival. Suitable sizes for portions of an ectoparasite saliva protein of the present invention are as disclosed for saliva protein homologues of the present invention.

As will be apparent to one of skill in the art, the present invention is intended to apply to all ectoparasites. A formulation of the present invention can include saliva products from any ectoparasites. A preferred

ectoparasite of the present invention from which to isolate saliva products (including proteins), and/or from which to identify proteins that can then be produced recombinantly or synthetically, include arachnids, insects and leeches.

5 More preferred ectoparasites from which to obtain saliva products include fleas; ticks, including both hard ticks of the family Ixodidae (e.g., *Ixodes* and *Amblyomma*) and soft ticks of the family Argasidae (e.g., *Ornithodoros*, such as *O. parkeri* and *O. turicata*); flies, such as midges (e.g., *Culicoides*), mosquitos, sand flies, black flies, horse flies, horn flies, deer flies, tsetse flies, stable flies, myiasis-causing flies and biting gnats; ants; spiders, lice; mites; and true bugs, such as bed bugs and kissing bugs, including those carrying Chagas disease. Even more preferred ectoparasite saliva products include those from fleas, mosquitos, midges, sandflies, blackflies, ticks and *Rhodnius*, with products from fleas, mosquitos and *Culicoides* being even more preferred.

A particularly preferred formulation of the present invention includes flea saliva proteins. Preferred flea saliva products include those from *Ctenocephalides*, *Xenopsylla*, *Pulex*, *Tunga*, *Nosopsyllus*, *Diamanus*, *Ctropsyllus* and *Echidnophaga* fleas, with saliva products from *Ctenocephalides canis* and *Ctenocephalides felis* fleas being even more preferred. For the purposes of illustration, many

of the following embodiments discuss flea saliva proteins. Such discussion of flea saliva proteins is not intended, in any way, to limit the scope of the present invention.

In another embodiment, a formulation of the present invention includes at least a portion of an ectoparasite saliva protein homologue having at least a portion of one of the following amino acid sequences: SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87 and/or other sequences disclosed herein.

In one embodiment, a formulation of the present invention can include at least one isolated protein having (i.e., including) at least a portion of one of the amino acid sequences identified in the Sequence ID Listing, and more specifically an amino acid sequence selected from the group consisting of SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87.

It is to be appreciated that ectoparasite saliva proteins of the present invention include, but are not limited to, full-length proteins, hybrid proteins, fusion proteins, multivalent proteins, and proteins that are truncated homologues of, or are proteolytic products of, at least a portion of a protein having at least a portion of one of the following amino acid sequences: SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ

ID NO:75, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:87 and/or other sequences disclosed herein. As used herein, the term hybrid protein refers to a single protein produced from two different proteins.

5           The foregoing SEQ ID NO's represent amino acid sequences deduced according to methods disclosed in the Examples. It should be noted that since amino acid sequencing technology is not entirely error-free, the foregoing SEQ ID NO's, at best, represent an apparent amino acid sequence of the ectoparasite saliva proteins of the present invention. In addition, the variation seen in the foregoing SEQ ID NO's can also be due, at least in part, to allelic variation since the proteins being sequenced were derived from populations of fleas.

10           According to the present invention, a formulation of the present invention can include flea saliva proteins that have undergone post-translational modification. Such modification can include, for example, glycosylation. Glycosylation can include addition of N-linked and/or O-linked oligosaccharides. It is to be appreciated that post-translational modification of a protein of the present invention can contribute to an epitope's ability to induce an allergic response against the protein in an immediate or delayed hypersensitivity response.

20           Another embodiment of the present invention is an isolated nucleic acid molecule capable of hybridizing,



under stringent conditions, with an ectoparasite saliva protein gene encoding an ectoparasite saliva protein of the present invention. In accordance with the present invention, an isolated nucleic acid molecule is a nucleic acid molecule that has been removed from its natural milieu (i.e., that has been subject to human manipulation). As such, "isolated" does not reflect the extent to which the nucleic acid molecule has been purified. An isolated nucleic acid molecule can include DNA, RNA, or derivatives of either DNA or RNA.

An isolated nucleic acid molecule of the present invention can be obtained from its natural source either as an entire (i.e., complete) gene or a portion thereof capable of forming a stable hybrid with that gene. As used herein, the phrase "at least a portion of" an entity refers to an amount of the entity that is at least sufficient to have the functional aspects of that entity. For example, at least a portion of a nucleic acid sequence, as used herein, is an amount of a nucleic acid sequence capable of forming a stable hybrid with the corresponding gene under stringent hybridization conditions. An isolated nucleic acid molecule of the present invention can also be produced using recombinant DNA technology (e.g., polymerase chain reaction (PCR) amplification, cloning) or chemical synthesis. Isolated ectoparasite saliva protein nucleic acid molecules include natural nucleic acid molecules and homologues

thereof, including, but not limited to, natural allelic variants and modified nucleic acid molecules in which nucleotides have been inserted, deleted, substituted, and/or inverted in such a manner that such modifications do not substantially interfere with the nucleic acid molecule's ability to encode an ectoparasite saliva protein of the present invention or to form stable hybrids under stringent conditions with natural nucleic acid molecule isolates.

An isolated nucleic acid molecule of the present invention can include a nucleic acid sequence that encodes at least one ectoparasite saliva protein of the present invention, examples of such proteins being disclosed herein. Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably, especially with respect to a nucleic acid molecule, or a nucleic acid sequence, being capable of encoding an ectoparasite saliva protein. As heretofore disclosed, ectoparasite saliva proteins of the present invention include, but are not limited to, proteins having full-length ectoparasite saliva protein coding regions, portions thereof, and other ectoparasite saliva protein homologues.

It is to be appreciated that an ectoparasite saliva protein of the present invention can be encoded by a full-length nucleic acid sequence which encodes a polyprotein. The polyprotein can be post-translationally processed into multiple proteins which are found in saliva. As used herein, an ectoparasite saliva protein gene includes all nucleic acid sequences related to a natural ectoparasite saliva protein gene such as regulatory regions that control production of an ectoparasite saliva protein encoded by that gene (such as, but not limited to, transcription, translation or post-translation control regions) as well as the coding region itself. A nucleic acid molecule of the present invention can be an isolated natural ectoparasite saliva protein nucleic acid molecule or a homologue thereof. A nucleic acid molecule of the present invention can include one or more regulatory regions, full-length or partial coding regions, or combinations thereof. The minimal size of an ectoparasite saliva protein nucleic acid molecule of the present invention is the minimal size capable of forming a stable hybrid under stringent hybridization conditions with a corresponding natural gene.

An ectoparasite saliva protein nucleic acid molecule homologue can be produced using a number of methods known to those skilled in the art (see, for example, Sambrook et al., *ibid.*). For example, nucleic acid molecules can be modified using a variety of techniques including, but not

limited to, classic mutagenesis techniques and recombinant DNA techniques, such as site-directed mutagenesis, chemical treatment of a nucleic acid molecule to induce mutations, restriction enzyme cleavage of a nucleic acid fragment, ligation of nucleic acid fragments, polymerase chain reaction (PCR) amplification and/or mutagenesis of selected regions of a nucleic acid sequence, synthesis of oligonucleotide mixtures and ligation of mixture groups to "build" a mixture of nucleic acid molecules and combinations thereof. Nucleic acid molecule homologues can be selected from a mixture of modified nucleic acids by screening for the function of the protein encoded by the nucleic acid (e.g., the ability of a homologue to elicit an allergic response in animals having allergic dermatitis or the ability of a homologue to act as an anti-coagulant) and/or by hybridization with isolated ectoparasite saliva protein nucleic acids under stringent conditions.

One embodiment of the present invention is an ectoparasite saliva protein nucleic acid molecule that encodes a protein having at least a portion of one or more of the following amino acid sequences: SEQ ID NO:1, as well as with the complements of any of these sequences or homologues thereof. Such preferred nucleic acid molecules can hybridize to the coding and/or complementary strand.

A preferred nucleic acid molecule of the present invention is capable of hybridizing under stringent

conditions to the coding strand and/or to the strand complementary to the coding strand of a nucleic acid molecule that encodes at least a portion of such a flea saliva protein or homologue thereof. A particularly preferred nucleic acid sequence is a nucleic acid sequence having at least about 65 percent, preferably at least about 75 percent, more preferably at least about 85 percent, and even more preferably at least about 95 percent homology with a nucleic acid sequence encoding at least a portion of one or more of the following amino acid sequences: SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and/or SEQ ID NO:87.

Such nucleic acid molecules can be a full-length gene and/or a nucleic acid molecule encoding a full-length protein, a hybrid protein, a fusion protein, a multivalent protein or a truncation fragment. More preferred nucleic acid molecules of the present invention comprise isolated nucleic acid molecules having a nucleic acid sequence as represented by SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76, a nucleic acid sequence encoding amino acid sequence SEQ ID NO:78 or SEQ ID NO:87, or other sequences disclosed herein.

SEQ ID NO:52, a nucleic acid sequence that includes about 595 nucleotides of the apparent gene encoding flea saliva protein fspG5 (denoted nfspG5<sub>595</sub>), encodes a protein of about 90 amino acids (denoted as PfspG5<sub>90</sub>), represented by SEQ ID NO:53. The entire translation product of fspG5 is apparently about 71 amino acids and is denoted SEQ ID NO:56. SEQ ID NO:61, a nucleic acid sequence that includes about 1007 nucleotides of the apparent gene encoding flea saliva protein fspI (denoted nfspI<sub>1007</sub>), encodes a protein of about 155 amino acids (denoted PfspI<sub>155</sub>), which is denoted SEQ ID NO:62. SEQ ID NO:64, a nucleic acid sequence that includes about 1205 nucleotides of the apparent gene encoding flea saliva protein fspN5 (denoted nfspN5<sub>1205</sub>), encodes a protein of about 353 amino acids (denoted PfspN5<sub>353</sub>), which is denoted SEQ ID NO:65. SEQ ID NO:71, a nucleic acid sequence that includes about 406 nucleotides of the apparent gene encoding a fspN6 flea saliva protein (denoted nfspN6<sub>406</sub>), encodes a protein of about 135 amino acids (denoted PfspN6<sub>135</sub>), which is denoted SEQ ID NO:72. SEQ ID NO:74, a nucleic acid sequence that includes about 420 nucleotides of the apparent gene encoding a fspJ flea saliva protein, encodes a protein of about 72 amino acids, which is denoted SEQ ID NO:75.

Knowing a nucleic acid molecule of an ectoparasite saliva protein of the present invention allows one skilled in the art to make copies of that nucleic acid molecule as

well as to obtain a nucleic acid molecule including additional portions of ectoparasite saliva protein-encoding genes (e.g., nucleic acid molecules that include the translation start site and/or transcription and/or translation control regions), and/or ectoparasite saliva protein nucleic acid molecule homologues. Knowing a portion of an amino acid sequence of an ectoparasite saliva protein of the present invention allows one skilled in the art to clone nucleic acid sequences encoding such an ectoparasite saliva protein. In addition, a desired ectoparasite saliva protein nucleic acid molecule can be obtained in a variety of ways including screening appropriate expression libraries with antibodies which bind to ectoparasite saliva proteins of the present invention; traditional cloning techniques using oligonucleotide probes of the present invention to screen appropriate libraries or DNA; and PCR amplification of appropriate libraries, or RNA or DNA using oligonucleotide primers of the present invention (genomic and/or cDNA libraries can be used). To isolate flea saliva protein nucleic acid molecules, preferred cDNA libraries include cDNA libraries made from unfed whole flea, fed whole flea, fed flea midgut, unfed flea midgut, and flea salivary gland. Techniques to clone and amplify genes are disclosed, for example, in Sambrook et al., *ibid.* The Examples section includes examples of the isolation of cDNA

sequences encoding flea saliva proteins of the present invention.

The present invention also includes nucleic acid molecules that are oligonucleotides capable of hybridizing, under stringent conditions, with complementary regions of other, preferably longer, nucleic acid molecules of the present invention that encode at least a portion of one or more of the following amino acid sequences: SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:87, or homologues thereof, such oligonucleotides can hybridize to the coding or non-coding strand of a double-stranded nucleic acid molecule. Certain preferred oligonucleotides are capable of hybridizing to nucleic acid molecules including nucleic acid sequences represented by SEQ ID NO:52, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:71, SEQ ID NO:74, a nucleic acid sequence that encodes SEQ ID NO:78 or SEQ ID NO:87, or complements thereof.

Oligonucleotides of the present invention can be RNA, DNA, or derivatives of either. The minimal size of such oligonucleotides is the size required to form a stable hybrid between a given oligonucleotide and the complementary sequence on another nucleic acid molecule of the present invention. Minimal size characteristics are disclosed herein. The size of the oligonucleotide must also be sufficient for the use of the oligonucleotide in



accordance with the present invention. Oligonucleotides of the present invention can be used in a variety of applications including, but not limited to, as probes to identify additional nucleic acid molecules, as primers to  
5 amplify or extend nucleic acid molecules or in therapeutic applications to inhibit, for example, expression of saliva proteins by ectoparasites. Such therapeutic applications include the use of such oligonucleotides in, for example, antisense-, triplex formation-, ribozyme- and/or RNA drug-  
10 based technologies. The present invention, therefore, includes such oligonucleotides and methods to interfere with the production of ectoparasite saliva proteins by use of one or more of such technologies.

The present invention also includes a recombinant  
15 vector, which includes an ectoparasite saliva protein nucleic acid molecule of the present invention inserted into any vector capable of delivering the nucleic acid molecule into a host cell. Such a vector contains heterologous nucleic acid sequences, that is nucleic acid  
20 sequences that are not naturally found adjacent to ectoparasite saliva protein nucleic acid molecules of the present invention. The vector can be either RNA or DNA, either prokaryotic or eukaryotic, and typically is a virus or a plasmid. Recombinant vectors can be used in the  
25 cloning, sequencing, and/or otherwise manipulating of ectoparasite saliva protein nucleic acid molecules of the

present invention. One type of recombinant vector, herein referred to as a recombinant molecule and described in more detail below, can be used in the expression of nucleic acid molecules of the present invention. Preferred recombinant  
5 vectors are capable of replicating in the transformed cell.

A preferred nucleic acid molecule to include in a recombinant vector of the present invention is a nucleic acid molecule that encodes at least a portion of one or more of the following amino acid sequences: SEQ ID NO:53,  
10 SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87, or other sequences disclosed herein, or homologues thereof, and nucleic acid molecules including at least a portion of a nucleic acid sequence represented by SEQ ID NO:52, SEQ ID  
15 NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:71, SEQ ID NO:74, a nucleic acid sequence that encodes SEQ ID NO:78 or SEQ ID NO:87, or other sequences disclosed herein, or complements thereof. A more preferred sequences to include in a recombinant vector include nfspG5<sub>595</sub>, nfspG5<sub>270</sub>  
20 nfspG5<sub>213</sub>, nfspI<sub>1007</sub>, nfspN5<sub>1205</sub>, nfspN5<sub>1089</sub> nfspN6<sub>406</sub> and nfspJ<sub>420</sub>.

Preferred recombinant molecules of the present invention include pCro-nfspG5<sub>213</sub> and pCro-nfspI<sub>474</sub>, the production of which are described in detail in the Examples  
25 section.

In one embodiment, an isolated ectoparasite saliva protein of the present invention is produced by culturing a cell capable of expressing the protein under conditions effective to produce the protein, and recovering the protein. A preferred cell to culture is a recombinant cell that is capable of expressing the ectoparasite saliva protein, the recombinant cell being produced by transforming a host cell with one or more nucleic acid molecules of the present invention. Transformation of a nucleic acid molecule into a cell can be accomplished by any method by which a nucleic acid molecule can be inserted into the cell. Transformation techniques include, but are not limited to, transfection, electroporation, microinjection, lipofection, adsorption, and protoplast fusion. A recombinant cell may remain unicellular or may grow into a tissue, organ or a multicellular organism. Transformed nucleic acid molecules of the present invention can remain extrachromosomal or can integrate into one or more sites within a chromosome of the transformed (i.e., recombinant) cell in such a manner that their ability to be expressed is retained. Preferred nucleic acid molecules with which to transform a host cell include one or more nucleic acid molecules that are as disclosed herein for including in recombinant vectors of the present invention.

Suitable host cells to transform include any cell that can be transformed and that can express the introduced

ectoparasite saliva protein. Such cells are, therefore, capable of producing ectoparasite saliva proteins of the present invention after being transformed with at least one nucleic acid molecule of the present invention. Host cells  
5 can be either untransformed cells or cells that are already transformed with at least one nucleic acid molecule. Suitable host cells of the present invention can include bacterial, fungal (including yeast), insect, animal and plant cells. Preferred host cells include bacterial,  
10 yeast, insect and mammalian cells, with bacterial (e.g., *E. coli*) and insect (e.g., *Spodoptera*) cells being particularly preferred.

A recombinant cell is preferably produced by transforming a host cell with one or more recombinant molecules, each comprising one or more nucleic acid  
15 molecules of the present invention operatively linked to an expression vector containing one or more transcription control sequences. The phrase operatively linked refers to insertion of a nucleic acid molecule into an expression  
20 vector in a manner such that the molecule is able to be expressed when transformed into a host cell. As used herein, an expression vector is a DNA or RNA vector that is capable of transforming a host cell and of effecting expression of a specified nucleic acid molecule.  
25 Preferably, the expression vector is also capable of

replicating within the host cell. Expression vectors can be either prokaryotic or eukaryotic, and are typically viruses or plasmids. Expression vectors of the present invention include any vectors that function (i.e., direct gene expression) in recombinant cells of the present invention, including in bacterial, fungal, insect, animal, and/or plant cells. As such, nucleic acid molecules of the present invention can be operatively linked to expression vectors containing regulatory sequences such as promoters, operators, repressors, enhancers, termination sequences, origins of replication, and other regulatory sequences that are compatible with the recombinant cell and that control the expression of nucleic acid molecules of the present invention. As used herein, a transcription control sequence includes a sequence which is capable of controlling the initiation, elongation, and termination of transcription. Particularly important transcription control sequences are those which control transcription initiation, such as promoter, enhancer, operator and repressor sequences. Suitable transcription control sequences include any transcription control sequence that can function in at least one of the recombinant cells of the present invention. A variety of such transcription control sequences are known to those skilled in the art. Preferred transcription control sequences include those which function in bacterial, yeast, helminth, insect and

mammalian cells, such as, but not limited to, *tac*, *lac*,  
*trp*, *trc*, *oxy-pro*, *omp/lpp*, *rrnB*, bacteriophage lambda ( $\lambda$ )  
(such as  $\lambda p_L$  and  $\lambda p_R$  and fusions that include such  
promoters), bacteriophage T7, T7lac, bacteriophage T3,  
5 bacteriophage SP6, bacteriophage SP01, metallothionein,  
alpha mating factor, *Pichia* alcohol oxidase, alphavirus  
subgenomic promoters (such as Sindbis virus subgenomic  
promoters), baculovirus, *Heliothis zea* insect virus,  
vaccinia virus, herpesvirus, poxvirus, adenovirus, simian  
10 virus 40, retrovirus actin, retroviral long terminal  
repeat, Rous sarcoma virus, heat shock, phosphate and  
nitrate transcription control sequences as well as other  
sequences capable of controlling gene expression in  
prokaryotic or eukaryotic cells. Additional suitable  
15 transcription control sequences include tissue-specific  
promoters and enhancers as well as lymphokine-inducible  
promoters (e.g., promoters inducible by interferons or  
interleukins). Transcription control sequences of the  
present invention can also include naturally occurring  
20 transcription control sequences naturally associated with  
a DNA sequence encoding an ectoparasite saliva protein.

Expression vectors of the present invention may also  
contain secretory signals (i.e., signal segment nucleic  
acid sequences) to enable an expressed ectoparasite saliva  
25 protein to be secreted from the cell that produces the

protein. Suitable signal segments include an ectoparasite saliva protein signal segment or any heterologous signal segment capable of directing the secretion of an ectoparasite saliva protein, including fusion proteins, of the present invention. Preferred signal segments include, but are not limited to, tissue plasminogen activator (t-PA), interferon, interleukin, growth hormone, histocompatibility and viral envelope glycoprotein signal segments.

Expression vectors of the present invention may also contain fusion sequences which lead to the expression of inserted nucleic acid molecules of the present invention as fusion proteins. Inclusion of a fusion sequence as part of an ectoparasite nucleic acid molecule of the present invention can enhance the stability during production, storage and/or use of the protein encoded by the nucleic acid molecule. Furthermore, a fusion segment can function as a tool to simplify purification of an ectoparasite saliva protein, such as to enable purification of the resultant fusion protein using affinity chromatography. A suitable fusion segment can be a domain of any size that has the desired function (e.g., increased stability and/or purification tool). It is within the scope of the present invention to use one or more fusion segments. Fusion segments can be joined to amino and/or carboxyl termini of an ectoparasite saliva protein. Linkages between fusion

segments and ectoparasite saliva proteins can be constructed to be susceptible to cleavage to enable straight-forward recovery of the ectoparasite saliva proteins. Fusion proteins are preferably produced by  
5 culturing a recombinant cell transformed with a fusion nucleic acid sequence that encodes a protein including the fusion segment attached to either the carboxyl and/or amino terminal end of an ectoparasite saliva protein.

A recombinant molecule of the present invention is a  
10 molecule that can include at least one of any nucleic acid molecule heretofore described operatively linked to at least one of any transcription control sequence capable of effectalveoli regulating expression of the nucleic acid molecule(s) in the cell to be transformed. A preferred  
15 recombinant molecule includes one or more nucleic acid molecules that are as disclosed herein for including in a recombinant vector of the present invention.

A recombinant cell of the present invention includes any cells transformed with at least one of any nucleic acid  
20 molecules of the present invention. A preferred recombinant cell is a cell transformed with at least one nucleic acid molecule that encode a protein having at least a portion of one or more of the following amino acid sequences: SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID  
25 NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:87, or other sequences disclosed herein,



or homologues thereof, and nucleic acid molecules including at least a portion of a nucleic acid sequence represented by SEQ ID NO:52, SEQ ID NO:58, SEQ ID NO:61, SEQ ID NO:64, SEQ ID NO:71, SEQ ID NO:74, a nucleic acid sequence that encodes SEQ ID NO:78 or SEQ ID NO:87, or other sequences disclosed herein, or complements thereof. Particularly preferred recombinant cells include *E. coli* transformed with at least one of the aforementioned nucleic acid molecules. Preferred recombinant cells of the present invention include *E. coli*:pCro-nfspG5<sub>213</sub> and *E. coli*:pCro-nfspI<sub>474</sub>.

It may be appreciated by one skilled in the art that use of recombinant DNA technologies can improve expression of transformed nucleic acid molecules by manipulating, for example, the number of copies of the nucleic acid molecules within a host cell, the efficiency with which those nucleic acid molecules are transcribed, the efficiency with which the resultant transcripts are translated, and the efficiency of post-translational modifications. Recombinant techniques useful for increasing the expression of nucleic acid molecules of the present invention include, but are not limited to, operatively linking nucleic acid molecules to high-copy number plasmids, integration of the nucleic acid molecules into one or more host cell chromosomes, addition of vector stability sequences to plasmids,

substitutions or modifications of transcription control signals (e.g., promoters, operators, enhancers), substitutions or modifications of translational control signals (e.g., ribosome binding sites, Shine-Dalgarno sequences), modification of nucleic acid molecules of the present invention to correspond to the codon usage of the host cell, deletion of sequences that destabilize transcripts, and use of control signals that temporally separate recombinant cell growth from recombinant protein production during fermentation. The activity of an expressed recombinant protein of the present invention may be improved by fragmenting, modifying, or derivatizing the resultant protein.

In accordance with the present invention, recombinant cells can be used to produce an ectoparasite saliva protein of the present invention by culturing such cells under conditions effective to produce such a protein, and recovering the protein. Effective conditions to produce a protein include, but are not limited to, appropriate media, bioreactor, temperature, pH and oxygen conditions that permit protein production. An appropriate, or effective, medium refers to any medium in which a cell of the present invention, when cultured, is capable of producing an ectoparasite saliva protein. Such a medium is typically an aqueous medium comprising assimilable carbohydrate, nitrogen and phosphate sources, as well as appropriate

salts, minerals, metals and other nutrients, such as vitamins. The medium may comprise complex nutrients or may be a defined minimal medium.

Cells of the present invention can be cultured in conventional fermentation bioreactors, which include, but are not limited to, batch, fed-batch, cell recycle, and continuous fermentors. Culturing can also be conducted in shake flasks, test tubes, microtiter dishes, and petri plates. Culturing is carried out at a temperature, pH and oxygen content appropriate for the recombinant cell. Such culturing conditions are well within the expertise of one of ordinary skill in the art.

Depending on the vector and host system used for production, resultant ectoparasite saliva proteins may either remain within the recombinant cell; be secreted into the fermentation medium; be secreted into a space between two cellular membranes, such as the periplasmic space in *E. coli*; or be retained on the outer surface of a cell or viral membrane. The phrase "recovering the protein" refers simply to collecting the whole fermentation medium containing the protein and need not imply additional steps of separation or purification. Ectoparasite saliva proteins of the present invention can be purified using a variety of standard protein purification techniques, such as, but not limited to, affinity chromatography, ion exchange

chromatography, filtration, electrophoresis, hydrophobic interaction chromatography, gel filtration chromatography, reverse phase chromatography, chromatofocusing and differential solubilization.

5 Ectoparasite saliva proteins are preferably retrieved in "substantially pure" form. As used herein, "substantially pure" refers to a purity that allows for the effective use of the protein as a therapeutic composition or diagnostic. For example, an animal being administered  
10 dosages of ectoparasite saliva protein isolated from a recombinant cell of the present invention should exhibit no substantial toxicity from contaminants mixed with the protein.

Ectoparasite saliva that is substantially free of  
15 contaminating material can be collected using a saliva collection apparatus of the present invention (disclosed in related PCT Patent Publication No. WO 96/11,271, published April 18, 1996, by Frank et al.; this publication is incorporated by reference herein in its entirety). The  
20 interior diameter of a preferred chamber of the present invention is preferably about 7.5 cm. The size of a collection means of the present invention is preferably larger than the open end of the 7.5 cm chamber, the size of the collection means is more preferably about 8 cm.

25 According to the present invention, ectoparasite saliva products can be extracted from a collection means

(described in related PCT Patent Publication No. WO 96/11,271) by contacting a collection means with a Tris buffer containing sodium chloride, alcohol and Tris. A more preferred extraction buffer includes 2.5 M NaCl, 5% IPA and 20 mM Tris, about pH 8.0 to about pH 8.3. Suitable extraction times for eluting proteins and other products from the collection means using the Tris buffer are described in detail in the Examples.

Further concentration of saliva proteins extracted from a collection means of the present invention can be performed by concentrating the extracted flea saliva product-containing solution using hydrophobic interaction chromatographic (HIC) resins. Suitable HIC resins include any resins that bind protein at high salt concentrations. Preferred HIC resins include, for example, butyl-, octyl- and phenyl-substrate conjugated resins. A more preferred resin includes a phenyl-sepharose resin. In a preferred embodiment, extracted flea saliva proteins contained in a Tris buffer of the present invention can be contacted with a HIC resin to bind the flea saliva proteins to the resin.

In accordance with the present invention, a "mimotope" refers to any compound that is able to mimic the ability of an isolated ectoparasite saliva protein of the present invention to carry out its function (e.g., anti-coagulation, anti-complement, vasodialators, proteases, acid phosphatases or detecting and/or treating the

hypersensitivity of an animal susceptible to or having allergic dermatitis). A mimetope can be a peptide that has been modified to decrease its susceptibility to degradation but that still retains the desired activity. Other examples of mimetopes include, but are not limited to, carbohydrate-based compounds, lipid-based compounds, nucleic acid-based compounds, natural organic compounds, synthetically derived organic compounds, anti-idiotypic antibodies and/or catalytic antibodies, or fragments thereof. Mimetopes of the present invention can also include non-proteinaceous portions of ectoparasite saliva products having allergenic and/or antigenic activity (e.g., carbohydrate moieties associated with ectoparasite saliva proteins). A mimetope can be obtained by, for example, screening libraries of synthetic compounds for compounds capable of altering the ability of ectoparasites to feed, or of detecting and/or treating allergic dermatitis resulting from the bites of ectoparasites. A mimetope can also be obtained by, for example, rational drug design. In a rational drug design procedure, the three-dimensional structure of a compound of the present invention can be analyzed by, for example, nuclear magnetic resonance (NMR) or x-ray crystallography. The three-dimensional structure can then be used to predict structures of potential mimetopes by, for example, computer modeling. The predicted mimetope structures can then be produced by, for example, chemical synthesis, recombinant

DNA technology, or by isolating a mimetope from a natural source (e.g., plants, animals, bacteria and fungi).

One embodiment of the present invention is an *in vivo* test that is capable of detecting whether an animal is hypersensitive to ectoparasite saliva products. An *in vivo* test of the present invention can initially be used to determine if an animal is hypersensitive to ectoparasite saliva products and then used to determine if an animal is hypersensitive to a particular ectoparasite saliva component, in particular to an ectoparasite saliva protein. An *in vivo* hypersensitivity test of the present invention is particularly useful for identifying animals susceptible to or having allergic dermatitis. An *in vivo* hypersensitivity test of the present invention is even more useful for identifying animals susceptible to or having FAD. A suitable *in vivo* hypersensitivity test of the present invention can be, but is not limited to, a skin test comprising administering (e.g., intradermally injecting or superficial scratching) an effective amount of a formulation containing at least one ectoparasite saliva product, or a mimetope thereof. Methods to conduct skin tests of the present invention are known to those of skill in the art and are briefly disclosed herein.

Suitable formulations to use in an *in vivo* skin test include one or more isolated ectoparasite saliva proteins of the present invention.

A suitable amount of ectoparasite saliva protein for use in a skin test of the present invention can vary widely depending on the allergenicity of the product used in the test and on the site at which the product is delivered. Suitable amounts of ectoparasite saliva proteins for use in a skin test of the present invention include an amount capable of forming reaction, such as a detectable wheal or induration (hardness) resulting from an allergic reaction to the product. Preferred amounts of ectoparasite saliva proteins for use in a skin test of the present invention range from about 1 nanogram (ng) to about 500 micrograms ( $\mu$ g), more preferably from about 5 ng to about 300  $\mu$ g, and even more preferably from about 10 ng to about 50  $\mu$ g of ectoparasite saliva proteins. It is to be appreciated by those of skill in the art that such amounts will vary depending upon the allergenicity of the protein(s) being administered.

According to the present invention, ectoparasite saliva proteins of the present invention can be combined with an immunopotentiator (e.g., carriers or adjuvants of the present invention as defined in detail below). A novel aspect, however, of the present invention is that an ectoparasite saliva protein of the present invention can



induce a hypersensitive response in the absence of an immunopotentiator.

A skin test of the present invention further comprises administering a control solution to an animal. A control solution can include a negative control solution and/or a positive control solution. A positive control solution of the present invention contains an effective amount of at least one compound known to induce a hypersensitive response when administered to an animal. A preferred compound for use as positive control solution includes, but is not limited to, histamine. A negative control solution of the present invention can comprise a solution that is known not to induce a hypersensitive response when administered to an animal. As such, a negative control solution can comprise a solution having compounds essentially incapable of inducing a hypersensitive response or simply a buffer used to prepare the formulation, such as saline. An example of a preferred negative control solution is phenolated phosphate buffered saline (available from Greer Laboratories, Inc., Lenoir, NC).

Hypersensitivity of an animal to one or more formulations of the present invention can be evaluated by measuring reactions (e.g., wheal size, induration or hardness; using techniques known to those skilled in the art) resulting from administration of one or more experimental sample(s) and control sample(s) into an animal

and comparing the reactions to the experimental sample(s) with reactions resulting from administration of one or more control solution. Preferred devices for intradermal injections include individual syringes. Preferred devices for scratching include devices that permit the administration of a number of samples at one time. The hypersensitivity of an animal can be evaluated by determining if the reaction resulting from administration of a formulation of the present invention is larger than the reaction resulting from administration of a negative control, and/or by determining if the reaction resulting from administration of the formulation is at least about the same size as the reaction resulting from administration of a positive control solution. As such, if an experimental sample produces a reaction greater than or equal to the size of a wheal produced by administration of a positive control sample to an animal, then, that animal is hypersensitive to the experimental sample. Conversely, if an experimental sample produces a reaction similar to the reaction produced by administration of a negative control sample to an animal, then that animal is not hypersensitive to the experimental sample.

Preferred wheal sizes for evaluation of the hypersensitivity of an animal range from about 16 mm to about 8 mm, more preferably from about 15 mm to about 9 mm,

and even more preferably from about 14 mm to about 10 mm in diameter.

Preferably, the ability or inability of an animal to exhibit an immediate hypersensitive response to a formulation of the present invention is determined by measuring wheal sizes from about 2 minutes to about 30 minutes after administration of a sample, more preferably from about 10 minutes to about 25 minutes after administration of a sample, and even more preferably about 15 minutes after administration of a sample.

Preferably, the ability or inability of an animal to exhibit a delayed hypersensitive response to a formulation of the present invention is determined by measuring induration and/or erythema from about 18 hours to about 30 hours after administration of a sample, more preferably from about 20 hours to about 28 hours after administration of a sample, and even more preferably, at about 24 hours after administration of a sample. A delayed hypersensitivity response can also be measured using other techniques such as by determining, using techniques known to those of skill in the art, the extent of cell infiltrate at the site of administration during the time periods defined directly above.

In a preferred embodiment, a skin test of the present invention comprises intradermally injecting into an animal at a given site an effective amount of a formulation that

includes at least one flea saliva protein of the present invention, and intradermally injecting an effective amount of a control solution into the same animal at a different site. It is within the scope of one of skill in the art to use devices capable of delivering multiple samples simultaneously at a number of sites, preferably enabling concurrent evaluation of numerous formulations. One preferred formulation comprises flea saliva products collected in accordance with the present invention. Also preferred are formulations comprising one or more recombinantly produced flea saliva proteins.

Suitable flea saliva proteins for use with a skin test of the present invention include proteins having an amino acid sequence such as is listed in the Sequence Listing herein, or homologues thereof. A preferred positive control sample can be a sample comprising histamine. A preferred negative control sample can be a sample comprising diluent.

Animals suitable and preferred to test for hypersensitivity to ectoparasite saliva proteins using a skin test of the present invention are disclosed herein. Particularly preferred animals to test with a skin test of the present invention include dogs, cats and horses, with dogs and cats being even more preferred.

Another embodiment of the present invention is an *in vitro* immunoabsorbent test that is capable of detecting the presence of an antibody capable of binding to one or more ectoparasite saliva proteins of the present invention by contacting a putative antibody-containing solution with a solution containing ectoparasite saliva proteins in such a manner that immunocomplexes can form and be detected. Thus, an *in vitro* immunoabsorbent test of the present invention is particularly useful for identifying animals susceptible to or having allergic dermatitis by demonstrating that an animal has been previously exposed to an ectoparasite saliva antigen and, therefore may be hypersensitive to further exposure to an ectoparasite saliva antigen.

According to the present invention, an *in vitro* hypersensitivity test of the present invention can be, but is not limited to, an immunoabsorbent test comprising: (a) contacting a formulation of the present invention with a body fluid from an animal under conditions sufficient for formation of an immunocomplex between the formulation and antibodies, if present, in the body fluid; and (b) determining the amount of immunocomplex formed, wherein formation of the immunocomplex indicates that the animal is susceptible to or has allergic dermatitis. The immunoabsorbent test is particularly useful for the detection of IgE antibodies in the body fluid, thereby

indicating immediate hypersensitivity in the animal. Determining the amount of immunocomplex formed can include the step of separating depending on the mode of detection. Immunoabsorbent assays can be a variety of protocols and  
5 can be set-up by those of skill in the art.

A preferred immunoabsorbent test of the present invention comprises a first step of coating one or more portions of a solid substrate with a suitable amount of one or more ectoparasite saliva proteins of the present  
10 invention or a mimetope thereof, and of coating one or more other portions of the (or another) solid substrate with a suitable amount of positive and/or negative control solutions of the present invention. A preferred solid substrate of the present invention can include, but is not  
15 limited to, an ELISA plate, a dipstick, a radioimmunoassay plate, agarose beads, plastic beads, immunoblot membranes and paper; a more preferred solid substrate includes an ELISA plate, a dipstick or a radioimmunoassay plate, with an ELISA plate and a dipstick being even more preferred.  
20 As used herein, a dipstick refers to any solid material having a surface to which antibodies can be bound, such solid material having a stick-like shape capable of being inserted into a test tube. Suitable and preferred flea saliva proteins for use with an *in vitro* hypersensitivity  
25 test of the present invention are as disclosed for a skin test of the present invention.

A second step of a preferred *in vitro* hypersensitivity test of the present invention comprises contacting the coated substrate with a body fluid, such as serum, plasma or whole blood, from an animal susceptible to allergic dermatitis in such a manner as to allow antibodies contained in the body fluid that are capable of binding to ectoparasite saliva products to bind to such products bound to the substrate to form immunocomplexes. Excess body fluid and antibodies are then washed from the substrate. In a preferred embodiment in which IgE antibodies in the body fluid are to be measured, the body fluid can be pretreated to remove at least some of the other isotypes of immunoglobulin and/or other proteins, such as albumin, present in the fluid. Such removal can include, but is not limited to, contacting the body fluid with a material, such as Protein G, to remove IgG antibodies and/or affinity purifying the IgE antibodies from other components of the body fluid by exposing the fluid to, for example, Concanavalin A (Con-A).

A third step of a preferred *in vitro* hypersensitivity test of the present invention comprises contacting the immunocomplexes bound to the substrate with a compound capable of binding to the immunocomplexes, such as a secondary antibody or other compound that is capable of binding to the heavy chain of allergy-related antibodies

produced by animals allergic to ectoparasites, in such a manner that the compound(s) can bind to the immunocomplexes. Preferred binding compounds include, but are not limited to, secondary antibodies capable of binding to the heavy chain of IgE antibodies and Fc receptors (FcR) that bind to IgE antibodies (i.e., epsilon FcR), including single chains of an FcR (e.g., the alpha chain of an epsilon FcR), as well as truncated forms with or without transmembrane domains. Preferred animals to test are disclosed herein. Compounds capable of binding to immunocomplexes are usually tagged with a label which enables the amount of compound bound to the antibody from the body fluid to be measured. Such labels include, but are not limited to, a radioactive label, an enzyme capable of producing a color reaction upon contact with a substrate, a fluorescent label, a chemiluminescent label, a chromophoric label or a compound capable of being bound by another compound. Preferred labels include, but are not limited to, fluorescein, radioisotopes, alkaline phosphatases, biotin, avidin, or peroxidases.

A fourth step of a preferred *in vitro* hypersensitivity test of the present invention comprises measuring the amount of detectable label bound to the solid substrate using techniques known to those of skill in the art. It is within the scope of the present invention that the amount of antibody from the body fluid bound to the substrate can



be determined using one or more layers of secondary antibodies or other binding compounds. For example, an untagged secondary antibody can be bound to a serum antibody and the untagged secondary antibody can then be bound by a tagged tertiary antibody.

A hypersensitive animal is identified by comparing the level of immunocomplex formation using samples of body fluid with the level of immunocomplex formation using control samples. An immunocomplex refers to a complex comprising an antibody and its ligand (i.e., antigen). As such, immunocomplexes form using positive control samples and do not form using negative control samples. As such, if a body fluid sample results in immunocomplex formation greater than or equal to immunocomplex formation using a positive control sample, then the animal from which the fluid was taken is hypersensitive to the ectoparasite saliva product bound to the substrate. Conversely, if a body fluid sample results in immunocomplex formation similar to immunocomplex formation using a negative control sample, then the animal from which the fluid was taken is not hypersensitive to the ectoparasite saliva product bound to the substrate.

A preferred embodiment of an *in vitro* hypersensitivity test of the present invention comprises the steps of: (a) contacting an ELISA plate, which is coated with a suitable amount of flea saliva extract (disclosed in related PCT

Patent Publication No. WO 96/11,271, published April 18, 1996, by Frank et al.; this publication is incorporated by reference herein in its entirety), including FS-1, FS-2, FS-3 and/or one or more flea saliva proteins (disclosed in  
5 related PCT Patent Publication No. WO 96/11,271 and disclosed herein), with serum, plasma or whole blood from an animal being tested for susceptibility to allergic dermatitis; and (b) identifying whether immunocomplexes are formed by step (a) by assaying for the presence of such  
10 immunocomplexes by (i) contacting the plate with an antibody that specifically binds to IgE or other compounds capable of binding to such immunocomplexes, such as an epsilon Fc receptor, and (ii) determining whether such an antibody or other compound is bound thereto. It should be  
15 noted that citing of specific embodiments does not preclude the use of a variety of other immunoassay protocols, including those in which a compound that binds IgE is coated onto a substrate; the substrate is then contacted with serum, plasma or whole blood; and binding of IgE by  
20 the compound is detected by the ability to bind flea saliva extracts or proteins of the present invention.

One embodiment of the present invention is a kit useful for identification of an animal susceptible to or having allergic dermatitis. As used herein, a suspect  
25 animal is an animal to be tested. A kit of the present invention comprises a formulation of the present invention

and a means for determining if an animal is susceptible to or has allergic dermatitis, in which the formulation is used to identify animals susceptible to or having allergic dermatitis. A means for determining if an animal is susceptible to or has allergic dermatitis can include an *in vivo* or *in vitro* hypersensitivity test of the present invention as described in detail above. A kit of the present invention further comprises at least one control solution such as those disclosed herein.

A preferred kit of the present invention comprises the elements useful for performing an immunoassay. A kit of the present invention can comprise one or more experimental samples (i.e., formulations of the present invention) and one or more control samples bound to at least one pre-packed dipstick or ELISA plate, and the necessary means for detecting immunocomplex formation (e.g., labeled secondary antibodies or other binding compounds, and any necessary solutions needed to resolve such labels, as described in detail above) between antibodies contained in the bodily fluid of the animal being tested and the proteins bound to the dipstick or ELISA plate. It is within the scope of the invention that the kit can comprise simply a formulation of the present invention and that the detecting means can be provided in another way.

An alternative preferred kit of the present invention comprises elements useful for performing a skin test. A kit of the present invention can comprise at least one pre-packed syringe and needle apparatus containing one or more experimental samples and/or one or more control samples.

It is within the scope of the present invention that two or more different *in vivo* and/or *in vitro* tests can be used in combination for diagnostic purposes. For example, the immediate hypersensitivity of an animal to an ectoparasite saliva allergen can be tested using an *in vitro* immunoabsorbent test capable of detecting IgE antibodies specific for an ectoparasite saliva allergen in the animal's bodily fluid. While most animals that display delayed hypersensitivity to an ectoparasite saliva allergen also display immediate hypersensitivity to the allergen, a small number of animals that display delayed hypersensitivity to an allergen do not display immediate hypersensitivity to the allergen. In such cases, following negative results from the IgE-specific *in vitro* test, the delayed hypersensitivity of the animal to an ectoparasite saliva allergen can be tested using an *in vivo* test of the present invention.

Another aspect of the present invention includes treating animals susceptible to or having allergic dermatitis, with a formulation of the present invention.

According to the present invention, the term treatment can refer to the regulation of a hypersensitive response by an animal to bites from ectoparasites. Regulation can include, for example, immunomodulation of cells involved in the animal's hypersensitive response or alteration of the ability of an ectoparasite to introduce allergens into an animal, for example by inhibiting the anti-coagulation activity of a saliva enzyme, thereby impairing the ability of the arthropod to penetrate the dermis of an animal and feed. Immunomodulation can include modulating the activity of molecules typically involved in an immune response (e.g., antibodies, antigens, major histocompatibility molecules (MHC) and molecules co-reactive with MHC molecules). In particular, immunomodulation refers to modulation of antigen:antibody interactions resulting in inflammatory responses, immunosuppression, and immunotolerization of cells involved in a hypersensitive response. Immunosuppression refers to inhibiting an immune response by, for example, killing particular cells involved in the immune response. Immunotolerization refers to inhibiting an immune response by anergizing (i.e., diminishing reactivity of a T cell to an antigen) particular cells involved in the immune response. Suitable and preferred ectoparasites against which to treat an animal are disclosed herein. A particularly preferred formulation of the present invention is used to treat FAD.

One embodiment of the present invention is a therapeutic composition that, when administered to an animal in an effective manner, is useful for immunomodulating the immune response of the animal (i.e., immunomodulating the animal) so as to block (i.e., to inhibit, reduce or substantially prevent) a hypersensitive response by the animal upon subsequent exposure to allergenic components transmitted through bites from ectoparasites. Such a therapeutic composition is useful for immunomodulating animals known to be hypersensitive to ectoparasite saliva products and animals susceptible to hypersensitive responses against ectoparasite saliva products.

One embodiment of the present invention is a therapeutic composition that includes de-sensitizing compounds capable of inhibiting an immune response to an ectoparasite saliva protein of the present invention. Such de-sensitizing compounds include blocking compounds, toleragens and/or suppressor compounds. Blocking compounds comprise compounds capable of modulating antigen:antibody interactions that can result in inflammatory responses, toleragens are compounds capable of immunotolerizing an animal, and suppressor compounds are capable of immunosuppressing an animal. A de-sensitizing compound of the present invention can be soluble or membrane-bound. Membrane-bound de-sensitizing compounds can be associated

with biomembranes, including cells, liposomes, planar membranes, cochleates or micelles. A soluble de-sensitizing compound of the present invention is useful for: (1) inhibiting a Type I hypersensitivity reaction by  
5 blocking IgE:antigen mediated de-granulation of mast cells; (2) inhibiting a Type III hypersensitivity reaction by blocking IgG:antigen complex formation leading to complement destruction of cells; and (3) inhibiting a Type IV hypersensitivity reaction by blocking T helper cell  
10 stimulation of cytokine secretion by macrophages. A membrane-bound de-sensitizing compound of the present invention is useful for: (1) inhibiting a Type II hypersensitivity reaction by blocking IgG:antigen complex formation on the surface of cells leading to complement  
15 destruction of cells; (2) inhibiting a Type II hypersensitivity reaction by blocking IgG regulated signal transduction in immune cells; and (3) inhibiting a Type IV hypersensitivity reaction by blocking T cytotoxic cell killing of antigen-bearing cells.

20 A de-sensitizing compound of the present invention can also be covalently linked to a ligand molecule capable of targeting the de-sensitizing compound to a specific cell involved in a hypersensitive response to ectoparasite saliva products. Appropriate ligands with which to link a  
25 de-sensitizing compound include, for example, at least a portion of an immunoglobulin molecule, cytokines, lectins,

heterologous allergens, CD8 molecules, CD4 molecules or major histocompatibility molecules (e.g., MHC class I or MHC class II molecules). Preferred portions of immunoglobulin molecules to link to a de-sensitizing compound include variable regions capable of binding to immune cell specific surface molecules and constant regions capable of binding to Fc receptors on immune cells, in particular IgE constant regions. Preferred CD8 molecules include at least the extracellular functional domains of the  $\beta$  chain of CD8. Preferred CD4 molecules include at least the extracellular functional domains of CD4. An immune cell refers to a cell involved in an immune response, in particular, cells having MHC class I or MHC class II molecules. Preferred immune cells include antigen presenting cells, T cells and B cells.

In one embodiment, a therapeutic composition of the present invention includes ectoparasite saliva products of the present invention, or mimetopes thereof. Preferred therapeutic compositions include formulations comprising ectoparasite saliva extracts or at least one ectoparasite saliva product (preferably protein) of the present invention or mimetopes thereof.

Suitable therapeutic compositions of the present invention for treating flea allergy dermatitis include flea saliva extracts (such as those disclosed in related PCT Patent Publication No. WO 96/11,271) and other formulations



including at least one flea saliva protein, or a mimetope thereof. Preferred therapeutic compositions include FS-1, FS-2 and/or FS-3 (such as those disclosed in related PCT Patent Publication No. WO 96/11,271) as well as at least a portion of at least one flea saliva protein that can be isolated from FS-1, FS-2 and/or FS-3. As such, preferred formulations for use as therapeutic compositions include FS-1, FS-2, FS-3, and/or at least a portion of one or more of the proteins having an amino acid sequence including SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87.

In another embodiment, a therapeutic composition can include ectoparasite products of the present invention associated with a suitable excipient. A therapeutic composition of the present invention can be formulated in an excipient that the animal to be treated can tolerate. Preferred excipients are capable of maintaining a product of the present invention in a form that is capable of being bound by cells involved in an allergic response in an animal such that the cells are stimulated to initiate or enhance an immune response. Examples of such excipients include water, saline, Ringer's solution, dextrose solution, Hank's solution, and other aqueous physiologically balanced salt solutions. Nonaqueous vehicles, such as fixed oils, sesame oil, ethyl oleate, or

triglycerides may also be used. Other useful formulations include suspensions containing viscosity enhancing agents, such as sodium carboxymethylcellulose, sorbitol, or dextran. Excipients can also contain minor amounts of additives, such as substances that enhance isotonicity and chemical stability. Examples of buffers include phosphate buffer, bicarbonate buffer and Tris buffer, while examples of preservatives include thimerosal, m- or o-cresol, formalin and benzyl alcohol. Standard formulations can either be liquid injectables or solids which can be taken up in a suitable liquid as a suspension or solution for injection. Thus, in a non-liquid formulation, the excipient can comprise dextrose, human serum albumin, preservatives, etc., to which sterile water or saline can be added prior to administration.

In another embodiment, a therapeutic composition of the present invention can also comprise a carrier or adjuvant, although it is to be appreciated that an advantage of saliva products of the present invention is that adjuvants and/or carriers are not required for administration. Adjuvants are typically substances that generally enhance the immune response of an animal to a specific antigen. Suitable adjuvants include, but are not limited to, cytokines, chemokines, and compounds that induce the production of cytokines and chemokines (e.g., granulocyte macrophage colony stimulating factor [GM-CSF],

macrophage colony stimulating factor [M-CSF], granulocyte colony stimulating factor [G-CSF], colony stimulating factor [CSF], erythropoietin [EPO], interleukin-2 [IL-2], interleukin-3 [IL-3], interleukin-5 [IL-5], interleukin-6 [IL-6], interleukin-7 [IL-7], interleukin-8 [IL-8], interleukin-10 [IL-10], interleukin-12 [IL-12], gamma interferon [IFN- $\gamma$ ], interferon gamma inducing factor [IGIF], transforming growth factor beta, RANTES [regulated upon activation, normal T cell expressed and presumably secreted], macrophage inflammatory proteins [e.g., MIP1 $\alpha$  and MIP1 $\beta$ ], and Leishmania elongation initiating factor [LeIF]; bacterial components (e.g., endotoxins, in particular superantigens, exotoxins and cell wall components); aluminum-based salts; calcium-based salts; silica; polynucleotides; toxoids; serum proteins, viral coat proteins; block copolymer adjuvants (e.g., Hunter's Titermax<sup>TM</sup> adjuvant [Vaxcel<sup>TM</sup>, Inc. Norcross, GA], Ribi adjuvants [Ribi ImmunoChem Research, Inc., Hamilton, MT]; and saponins and their derivatives (e.g., Quil A [Superfos Biosector A/S, Denmark]). Protein adjuvants of the present invention can be delivered in the form of the protein themselves or of nucleic acid molecules encoding such proteins using the methods described herein.

Carriers are typically compounds that increase the half-life of a therapeutic composition in the treated animal. Suitable carriers include, but are not limited to,

polymeric controlled release formulations, biodegradable implants, liposomes, bacteria, viruses, oils, esters, and glycols.

One embodiment of the present invention is a controlled release formulation that is capable of slowly releasing a therapeutic composition of the present invention into the bloodstream of an animal. Suitable controlled release formulations include, but are not limited to, biocompatible (including biodegradable) polymers, other polymeric matrices, capsules, microcapsules, microparticles, bolus preparations, osmotic pumps, diffusion devices, liposomes, lipospheres, and transdermal delivery systems. Other controlled release formulations of the present invention include liquids that, upon administration to an animal, form a solid or a gel *in situ*.

The present invention also includes a recombinant virus particle therapeutic composition. Such a composition includes a recombinant molecule of the present invention that is packaged in a viral coat and that can be expressed in an animal after administration. Preferably, the recombinant molecule is packaging-deficient. A number of recombinant virus particles can be used, including, but not limited to, those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, and retroviruses. Preferred

recombinant particle viruses are those based on alphaviruses (such as Sindbis virus), herpesviruses and poxviruses. Methods to produce and use recombinant virus particle vaccines are disclosed in U.S. Patent Application  
5 Serial No. 08/015/414, filed February 8, 1993, entitled "Recombinant Virus Particle Vaccines", U.S. Patent No. 5,266,313, by Esposito et al., issued November 30, 1993 and U.S. Patent Application Serial No. 08/602,010, by Haanes et al., filed January 15, 1996, entitled "Recombinant Canine  
10 Herpesvirus", each of the patents and patent application referred to in this section is incorporated by reference herein in its entirety.

When administered to an animal, a recombinant virus particle therapeutic composition of the present invention  
15 infects cells within the immunized animal and directs the production of a protective protein or RNA nucleic acid molecule that is capable of protecting the animal from allergic dermatitis caused by the bites of ectoparasites. For example, a recombinant virus particle comprising a  
20 nucleic acid molecule encoding one or more ectoparasite saliva protein of the present invention is administered according to a protocol that results in the tolerization of an animal against ectoparasite saliva allergens.

According to one embodiment, a nucleic acid molecule  
25 of the present invention can be delivered to an animal as a naked (i.e., not packaged in a viral coat or cellular

membrane) nucleic acid vaccine (e.g., as naked DNA or RNA molecules, such as is taught, for example in Wolff et al., 1990, *Science* 247, 1465-1468). A naked nucleic acid vaccine of the present invention includes a nucleic acid molecule of the present invention and preferably includes a recombinant molecule of the present invention that preferably is replication, or otherwise amplification, competent. A naked nucleic acid vaccine of the present invention can comprise one or more nucleic acid molecules of the present invention in the form of, for example, a dicistronic recombinant molecule. Preferred naked nucleic acid vaccines include at least a portion of a viral genome (i.e., a viral vector). Preferred viral vectors include those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, and retroviruses, with those based on alphaviruses (such as Sindbis or Semliki virus), species-specific herpesviruses and species-specific poxviruses being particularly preferred. Any suitable transcription control sequence can be used, including those disclosed as suitable for protein production. Particularly preferred transcription control sequence include cytomegalovirus intermediate early (preferably in conjunction with Intron-A), Rous Sarcoma Virus long terminal repeat, and tissue-specific transcription control sequences, as well as transcription control sequences endogenous to viral vectors

if viral vectors are used. The incorporation of "strong" poly(A) sequences are also preferred.

Naked nucleic acid vaccines of the present invention can be administered in a variety of ways, with intramuscular, subcutaneous, intradermal, transdermal, intranasal and oral routes of administration being preferred. An example of one embodiment is disclosed in PCT Patent Publication No. WO 95/05853, published March 2, 1995. A preferred single dose of a naked nucleic acid vaccine ranges from about 1 nanogram (ng) to about 100 µg, depending on the route of administration and/or method of delivery, as can be determined by those skilled in the art. Suitable delivery methods include, for example, by injection, as drops, aerosolized, oral and/or topical. Naked DNA of the present invention can be contained in an aqueous excipient (e.g., phosphate buffered saline) alone or a carrier (e.g., lipid-based vehicles).

Therapeutic compositions of the present invention can be sterilized by conventional methods which do not result in protein degradation (e.g., filtration) and/or lyophilized.

A therapeutic composition of the present invention can be administered to any animal susceptible to ectoparasite infestation as herein described. Acceptable protocols by which to administer therapeutic compositions of the present invention in an effective manner can vary according to

individual dose size, number of doses, frequency of dose administration, and mode of administration. Determination of such protocols can be accomplished by those skilled in the art. An effective dose refers to a dose capable of treating an animal against hypersensitivity to ectoparasite saliva allergens. Effective doses can vary depending upon, for example, the therapeutic composition used, the arthropod from which the composition was derived, and the size and type of the recipient animal. Effective doses to immunomodulate an animal against ectoparasite saliva allergens include doses administered over time that are capable of alleviating a hypersensitive response by an animal to ectoparasite saliva allergens. For example, a first tolerizing dose can comprise an amount of a therapeutic composition of the present invention that causes a minimal hypersensitive response when administered to a hypersensitive animal. A second tolerizing dose can comprise a greater amount of the same therapeutic composition than the first dose. Effective tolerizing doses can comprise increasing concentrations of the therapeutic composition necessary to tolerize an animal such that the animal does not have a hypersensitive response to the bite of an ectoparasite. An effective dose to desensitize an animal can comprise a concentration of a therapeutic composition of the present invention sufficient to block an animal from having a hypersensitive response to the bite of



an ectoparasite. Effective desensitizing doses can include repeated doses having concentrations of a therapeutic composition that cause a minimal hypersensitive response when administered to a hypersensitive animal.

5 A suitable single dose is a dose that is capable of treating an animal against hypersensitivity to ectoparasite saliva allergens when administered one or more times over a suitable time period. For example, a preferred single dose of an ectoparasite saliva product, or mimetope  
10 therapeutic composition is from about 0.5 ng to about 1 g of the therapeutic composition per kilogram body weight of the animal. Further treatments with the therapeutic composition can be administered from about 1 hour to 1 year after the original administration. Further treatments with  
15 the therapeutic composition preferably are administered when the animal is no longer protected from hypersensitive responses to ectoparasite. Particular administration doses and schedules can be developed by one of skill in the art based upon the parameters discussed above. Modes of  
20 administration can include, but are not limited to, subcutaneous, intradermal, intravenous, nasal, oral, transdermal and intramuscular routes.

A therapeutic composition of the present invention can be used in conjunction with other compounds capable of  
25 modifying an animal's hypersensitivity to ectoparasite bites. For example, an animal can be treated with compounds

capable of modifying the function of a cell involved in a hypersensitive response, compounds that reduce allergic reactions, such as by systemic agents or anti-inflammatory agents (e.g., anti-histamines, anti-steroid reagents, anti-inflammatory reagents and reagents that drive immunoglobulin heavy chain class switching from IgE to IgG). Suitable compounds useful for modifying the function of a cell involved in a hypersensitive response include, but are not limited to, antihistamines, cromolyn sodium, theophylline, cyclosporin A, adrenalin, cortisone, compounds capable of regulating cellular signal transduction, compounds capable of regulating adenosine 3',5'-cyclic phosphate (cAMP) activity, and compounds that block IgE activity, such as peptides from IgE or IgE specific Fc receptors, antibodies specific for peptides from IgE or IgE-specific Fc receptors, or antibodies capable of blocking binding of IgE to Fc receptors.

Another aspect of the present invention includes a method for prescribing treatment for animals susceptible to or having allergic dermatitis, using a formulation of the present invention. A preferred method for prescribing treatment for flea allergy dermatitis, for example, comprises: (1) intradermally injecting into an animal at one site an effective amount of a formulation containing at least one flea saliva antigen of the present invention, or a mimetope thereof (suitable and preferred formulations are

disclosed herein); (2) intradermally injecting into the animal at a second site an effective amount of a control solution; (3) evaluating if the animal has flea allergy dermatitis by measuring and comparing the wheal size resulting from injection of the formulation with the wheal size resulting from injection of the control solution; and (4) prescribing a treatment for the flea allergy dermatitis.

An alternative preferred method for prescribing treatment for flea allergy dermatitis comprises: (1) contacting a first portion of a sample of bodily fluid obtained from an animal to be tested with an effective amount of a formulation containing at least one flea saliva antigen, or a mimetope thereof (suitable and preferred formulations are disclosed herein) to form a first immunocomplex solution; (2) contacting a positive control antibody to form a second immunocomplex solution; (3) evaluating if the animal has flea allergy dermatitis by measuring and comparing the amount of immunocomplex formation in the first and second immunocomplex solutions; and (4) prescribing a treatment for the flea allergy dermatitis. It is to be noted that similar methods can be used to prescribe treatment for allergies caused by other ectoparasites using ectoparasite saliva product formulations as disclosed herein.

Another aspect of the present invention includes a method for monitoring animals susceptible to or having allergic dermatitis, using a formulation of the present invention. *In vivo* and *in vitro* tests of the present invention can be used to test animals for allergic dermatitis prior to and following any treatment for allergic dermatitis. A preferred method to monitor treatment of flea allergy dermatitis (which can also be adapted to monitor treatment of other ectoparasite allergies) comprises: (1) intradermally injecting an animal at one site with an effective amount of a formulation containing at least one flea saliva protein, or a mimetope thereof (suitable and preferred formulations are disclosed herein); (2) intradermally injecting an effective amount of a control solution into the animal at a second site; and (3) determining if the animal is desensitized to flea saliva antigens by measuring and comparing the wheal size resulting from injection of the formulation with the wheal size resulting from injection of the control solution.

An alternative preferred method to monitor treatment of flea allergy dermatitis (which can be adapted to monitor treatments of other ectoparasite allergies) comprises: (1) contacting a first portion of a sample of bodily fluid obtained from an animal to be tested with an effective amount of a formulation containing at least one flea saliva protein or mimetope thereof (suitable and preferred

formulations are disclosed herein) to form a first immunocomplex solution; (2) contacting a positive control antibody to form a second immunocomplex solution; and (3) determining if the animal is desensitized to flea saliva antigens by measuring and comparing the amount of immunocomplex formation in the first and second immunocomplex solutions.

The present invention also includes antibodies capable of selectively binding to an ectoparasite saliva protein, or mimetope thereof. Such an antibody is herein referred to as an anti-ectoparasite saliva protein antibody. As used herein, the term "selectively binds to" refers to the ability of such an antibody to preferentially bind to ectoparasite saliva proteins and mimetopes thereof. In particular, the present invention includes antibodies capable of selectively binding to flea saliva proteins. Binding can be measured using a variety of methods known to those skilled in the art including immunoblot assays, immunoprecipitation assays, enzyme immunoassays (e.g., ELISA), radioimmunoassays, immunofluorescent antibody assays and immunoelectron microscopy; see, for example, Sambrook et al., *ibid*.

Antibodies of the present invention can be either polyclonal or monoclonal antibodies. Antibodies of the present invention include functional equivalents such as antibody fragments and genetically-engineered antibodies,

including single chain antibodies, that are capable of selectively binding to at least one of the epitopes of the protein or mimetope used to obtain the antibodies. Preferably, an antibody of the present invention has a  
5 single site binding affinity of from about  $10^3 \text{ M}^{-1}$  to about  $10^{12} \text{ M}^{-1}$  for a flea saliva product of the present invention.

A preferred method to produce antibodies of the present invention includes administering to an animal an effective amount of an ectoparasite saliva protein or  
10 mimetope thereof to produce the antibody and recovering the antibodies. Antibodies raised against defined proteins or mimetopes can be advantageous because such antibodies are not substantially contaminated with antibodies against other substances that might otherwise cause interference in  
15 a diagnostic assay or side effects if used in a therapeutic composition.

Antibodies of the present invention have a variety of potential uses that are within the scope of the present invention. For example, such antibodies can be used (a) as  
20 vaccines to passively immunize an animal in order to protect the animal from allergic dermatitis, (b) as positive controls in test kits, and/or (c) as tools to recover desired ectoparasite saliva proteins from a mixture of proteins and other contaminants.

The following examples are provided for the purposes of illustration and are not intended to limit the scope of the present invention.

#### EXAMPLES

5 It is to be noted that the Examples include a number of molecular biology, microbiology, immunology and biochemistry techniques considered to be known to those skilled in the art. Disclosure of such techniques can be found, for example, in Sambrook et al., *ibid.*, Borovsky, Arch. Insect Biochem. and Phys., 7:187-210, 1988, and related references. Examples 1 through 16, and the SEQ ID NO's cited therein, of related PCT Publication WO 96/11,271, published April 18, 1996, are incorporated herein by this reference in their entirety.

10  
15 Example 1

This example describes the amino acid sequence analysis of additional isolated flea saliva proteins from FS-1 extract and eluted from DE-81 filters.

20 FS-1 flea saliva extract and flea saliva product eluted from DE-81 filters were collected using techniques described in Example 2 of related PCT Publication No. WO 96/11,271. Using standard purification techniques (e.g., C4 reverse phase chromatography; SDS-PAGE gel electrophoresis and blotting; and/or flow through  
25 electrophoresis), several proteins were isolated from peak

M and partial amino acid sequences were determined as described in Example 4 of related PCT Publication No. WO 96/11,271. Partial N-terminal amino acid sequencing indicated that peak M contained fspJ, fspL and fspN proteins (as described in Example 4 of related PCT Publication No. WO 96/11,271) as well as newly identified proteins referred to herein as fspM(G), fspM(H), fspM(I), fspM(J), fspM(K), fspM(L) and fspM(M). Flea saliva protein fspM(G), having a molecular weight of about 37 kD, had an N-terminal partial amino acid sequence of M R G N H V F L E D G M A D M T G G Q Q M G R D L Y, denoted SEQ ID NO:1. Flea saliva protein fspM(H), having a molecular weight of about 34 kD, had an N-terminal partial amino acid sequence of K Y R N (Y/D) X T N D P Q Y, denoted SEQ ID NO:2. Flea saliva protein fspM(I), having a molecular weight of about 10 kD had an N-terminal partial amino acid sequence of E I K R N D R E P G N L S K I R T V M D K V, I K Q T Q, denoted SEQ ID NO:3. Flea saliva protein fspM(J), having a molecular weight of about 25 kD, had an N-terminal partial amino acid sequence of L K D N D I Y (A/H) (A/H) R D I N E I L R V L D P S K, denoted SEQ ID NO:4. Flea saliva protein fspM(K), having a molecular weight of about 30 kD, had an N-terminal partial amino acid sequence of N Y G R V Q I E D Y T X S N H K D X E E K D Q I N G L, denoted SEQ ID NO:5. Flea saliva protein fspM(L), having a molecular weight of about 37 kD, had an N-terminal partial amino acid



sequence of K Y R N X Y T N D P Q L K L L D E G, denoted  
SEQ ID NO:6. Flea saliva protein fspM(M) was recovered  
from peak M and subjected to amino acid sequence analysis  
as described in Example 4 of related PCT Publication No. WO  
5 96/11,271. Flea saliva protein fsp(M), having a molecular  
weight of about 31 kD, had an N-terminal partial amino acid  
sequence of Y F N D Q I K S V M E P X V F K Y P X A X L,  
denoted SEQ ID NO:7. A Genbank homology search revealed no  
significant homology between known amino acid sequences and  
those determined for fspM(G), fspM(H), fspM(I), fspM(J),  
10 fspM(K), fspM(L) and fspM(M).

#### Example 2

This example describes the isolation of nucleic acid  
molecules encoding at least a portion of a fspG flea saliva  
protein. This example also describes expression of a fspG  
15 protein by bacteria.

##### A. Isolation of fspG4 nucleic acid molecules

The partial N-terminal amino acid sequence of fspG2  
(i.e., SEQ ID NO:29 of related PCT Publication No. WO  
20 96/11,271) was used to synthesize degenerate antisense  
Primer G2-2, having the nucleic acid sequence 5' TGR TTT  
CCW ATR AAR TCT TC 3', denoted SEQ ID NO:8. Primer G2-2  
was used in combination with the M13 reverse primer (SEQ ID  
NO:40; described in Example 7 of related PCT Publication  
25 No. WO 96/11,271), to PCR amplify, using standard  
techniques, the 5'-terminal portion of the fspG4 gene from

a salivary gland cDNA expression library as described above in Example 6A of related PCT Publication No. WO 96/11,271. The resulting PCR product was approximately 225-bp when visualized on a 1% agarose gel. The nucleotide sequence of the 225-bp PCR fragment was obtained, named nfspG4<sub>225</sub> is presented as SEQ ID NO:9.

The nucleic acid sequence of nfspG4<sub>225</sub> was used to synthesize sense Primer G5, having nucleic acid sequence 5' AAT TCG GCA CGA GTG 3', denoted SEQ ID NO:10. Primer G5 was used in combination with the M13 universal primer (SEQ ID NO:19; described in Example 6 of related PCT Publication No. WO 96/11,271), to PCR amplify, as described above, the 3'-terminal portion of the fspG4 gene from the salivary gland cDNA expression library described above in Example 6A of related PCT Publication No. WO 96/11,271). The resulting PCR product, denoted nfspG4<sub>610</sub>, was approximately 610-bp when visualized on a 1% agarose gel. The nucleotide sequence of the 610-bp PCR fragment was obtained, 565 nucleotides of which are presented as SEQ ID NO:11. The nucleic acid molecule containing nucleic acid sequence SEQ ID NO:11 is referred to herein as nfspG4<sub>565</sub>. Translation of SEQ ID NO:11 suggests that nucleic acid molecule nfspG4<sub>565</sub> encodes a full-length fspG protein of about 90 amino acids, referred to herein as PfspG4<sub>90</sub>, assuming an open reading frame having a start codon spanning from about nucleotide 45 through about nucleotide

47 of SEQ ID NO:11 and a stop codon spanning from about nucleotide 315 through about nucleotide 317 of SEQ ID NO:11. This open reading frame, excluding the stop codon, comprises nucleic acid molecule nfspG4<sub>270</sub> of the present invention, the nucleic acid sequence of which is represented herein by SEQ ID NO:13. PfspG4<sub>90</sub> is denoted herein as SEQ ID NO:12. Residues 20-42 of SEQ ID NO:12 appear to be identical to SEQ ID NO:29 of related PCT Publication No. WO 96/11,271 (N-terminal partial amino acid sequence of fspG2), except that residue 37 of SEQ ID NO:12 is a glutamic acid rather than a lysine. In addition, residues 38-57 of SEQ ID NO:12 appear to be identical to SEQ ID NO:30 of related PCT Publication No. WO 96/11,271 (N-terminal partial amino acid sequence of fspG3). These similarities support the likelihood of a family of fspG proteins in flea saliva.

Analysis of SEQ ID NO:11 suggests that the sequence includes a leader segment of about 19 amino acids followed by a mature protein. The leader sequence is apparently cleaved to form a mature protein termed PfspG4<sub>71</sub>, denoted SEQ ID NO:12. PfspG4<sub>71</sub> has a calculated molecular weight of 7536 daltons and calculated pI of about 9.0. PfspG4<sub>90</sub> has a calculated molecular weight of 9657 daltons and calculated pI of about 9.26. A Genbank homology search revealed no significant homology between SEQ ID NO:11 or SEQ ID NO:12

and known nucleic acid sequences or known amino acid sequences, respectively.

#### B. Expression

An about 216-bp DNA fragment of nfspG4 was PCR amplified from nucleic acid molecule nfspG4, using: Primer G7, a sense primer having the nucleic acid sequence 5' AGT GGA TCC GTC AAA AAT GGT CAC TG 3', denoted as (SEQ ID NO:15 (BamHI site in bold); and Primer G8, an antisense primer having the nucleic acid sequence 5' CCG GAA TTC GGT TAT TCG CAA TAA CAG T 3' (EcoRI site in bold), denoted SEQ ID NO:16. The PCR product, a fragment of about 216 nucleotides, denoted nfspG4<sub>216</sub>, was digested with BamHI and EcoRI restriction endonucleases, gel purified, and subcloned into expression vector P<sub>R</sub>/T<sup>2</sup>ori/S10HIS-RSET-A9 (described in Example 16 of related PCT Publication No. WO 96/11,271) that had been digested with BamHI and EcoRI to produce recombinant molecule pHis-nfspG4<sub>216</sub>.

The recombinant molecule was transformed into *E. coli* to form recombinant cell *E. coli*:pHis-nfspG4<sub>216</sub>. The recombinant cell was cultured and induced as described in Example 11A of related PCT Publication No. WO 96/11,271 to produce fusion protein PHIS-fspG4<sub>72</sub>. The recombinant fusion protein was detected by immunoblot analysis using the T7 Tag monoclonal antibody as described in Example 11A of related PCT Publication No. WO 96/11,271.

Example 3

This example describes the isolation of nucleic acid sequences encoding at least a portion of flea saliva proteins fspM(A), fspM(B), fspM(C), fspM(D), fspM(E), and fspM(F).

A. nfspM(A)<sub>897</sub> and nfspM(B)<sub>2706</sub>

A flea salivary gland cDNA library (prepared as described in Example 6 of related PCT Publication No. WO 96/11,271) was immunoscreened with antiserum collected from a rabbit that was immunized with the proteins in peak M2 of the HPLC separation of flea saliva extract described in Example 3 of related PCT Publication No. WO 96/11,271 (i.e., fspM2 proteins). Immunoscreening was performed as described in Example 12 of related PCT Publication No. WO 96/11,271.

A nucleotide sequence for a nfspM nucleic acid molecule named nfspM(A)<sub>897</sub> is denoted as SEQ ID NO:17. Translation of SEQ ID NO:17 suggests that nucleic acid molecule nfspM(A)<sub>897</sub> encodes a full-length fspM protein of about 157 amino acids, referred to herein as PfspM(A)<sub>157</sub>, assuming an open reading frame having a start codon spanning from about nucleotide 97 through about nucleotide 99 of SEQ ID NO:17 and a stop codon spanning from about nucleotide 568 through about nucleotide 570 of SEQ ID NO:17. This open reading frame, excluding the stop codon, comprises nucleic acid molecule nfspM(A)<sub>471</sub> of the present

invention, the nucleic acid sequence of which is represented herein by SEQ ID NO:19. The amino acid sequence of PfspM(A)<sub>157</sub> is denoted SEQ ID NO:18. PfspM(A)<sub>157</sub> has a calculated molecular weight of about 18,291.68 daltons and calculated pI of about 10.3. A Genbank homology search revealed no significant homology between SEQ ID NO:17 or SEQ ID NO:18 and known nucleic acid or amino acid sequences, respectively.

A nucleotide sequence for another nfspM nucleic acid molecule named nfspM(B)<sub>2706</sub> is denoted as SEQ ID NO:20. Translation of SEQ ID NO:20 suggests that nucleic acid molecule nfspM(B)<sub>2706</sub> encodes a non-full-length fspM protein of about 900 amino acids, referred to herein as PfspM(B)<sub>900</sub>, assuming an open reading frame having a start codon spanning from about nucleotide 5 through about nucleotide 7 of SEQ ID NO:20. The amino acid sequence of PfspM(B)<sub>900</sub> is denoted SEQ ID NO:21. PfspM(B)<sub>900</sub> has a calculated molecular weight of about 104,647 daltons and calculated pI of about 5.8.

The nucleic acid and amino acid sequences of the nfspM(B)<sub>2706</sub> nucleic acid molecule and PfspM(B)<sub>900</sub> protein, respectively, were compared to known nucleic acid and amino acid sequences using a Genbank homology search. SEQ ID NO:21 was found to be similar to the amino acid sequence of RhoA-binding alpha kinase (ROK). The most highly conserved region of continuous similarity between SEQ ID NO:21 and

ROK amino acid sequences spans from about amino acid 32 through about amino acid 351 of SEQ ID NO:21 and from about amino acid 1 through about amino acid 900 of the ROK, there being about 75% identity between the two regions.

5 Comparison of the nucleic acid sequence encoding amino acids from about 326 through about 1285 of the ROK kinase with the corresponding regions, spanning nucleotides from about 98 through about 1075 of nfspM(B)<sub>2706</sub> indicate that those regions are about 71% identical.

10 B. nfspM(C)<sub>414</sub> and nfspM(D)<sub>273</sub>

A flea salivary gland cDNA library (prepared as described in Example 6 of related PCT Publication No. WO 96/11,271) was immunoscreened with antiserum collected from a rabbit that was immunized with the proteins in peak M1 of the HPLC separation of flea saliva extract described in  
15 Example 3 of related PCT Publication No. WO 96/11,271 (i.e., fspM1 proteins). Immunoscreening was performed as described in Example 12 of related PCT Publication No. WO 96/11,271.

20 Nucleotide sequence for a nfspM nucleic acid molecule named nfspM(C)<sub>414</sub> is denoted as SEQ ID NO:22. Translation of SEQ ID NO:22 suggests that nucleic acid molecule nfspM(C)<sub>414</sub> encodes a non-full-length fspM protein of about 137 amino acids, referred to herein as PfspM(C)<sub>137</sub>, assuming  
25 the first residue spans from about nucleotide 2 through about nucleotide 4 of SEQ ID NO:22. The amino acid

sequence of PfspM(C)<sub>137</sub> is denoted SEQ ID NO:23. PfspM(C)<sub>137</sub> has a calculated molecular weight of about 14,452 daltons and calculated pI of about 2.81. A Genbank homology search revealed no significant homology between SEQ ID NO:22 or  
5 SEQ ID NO:23 and known nucleic acid sequences or known amino acid sequences, respectively.

A nucleotide sequence for another nfspM nucleic acid molecule named nfspM(D)<sub>273</sub> is denoted as SEQ ID NO:24. Translation of SEQ ID NO:24 suggests that nucleic acid  
10 molecule nfspM(D)<sub>273</sub> encodes a non-full-length fspM protein of about 90 amino acids, referred to herein as PfspM(D)<sub>90</sub>, assuming the first residue spans from about nucleotide 3 through about nucleotide 5 of SEQ ID NO:24. The amino acid sequence of PfspM(D)<sub>90</sub> is denoted SEQ ID NO:25. PfspM(D)<sub>90</sub>  
15 has a calculated molecular weight of about 9,503 daltons and calculated pI of about 3.01. SEQ ID NO:24 and SEQ ID NO:25 appear to be substantially similar to SEQ ID NO:22 and SEQ ID NO:23, respectively, suggesting a family of fspM proteins in flea saliva.

20 C. nfspM(E)<sub>1704</sub> and nfspM(F)<sub>1758</sub>

A flea salivary gland cDNA library (prepared as described in Example 6 as described of related PCT Publication No. WO 96/11,271) was immunoscreened with  
25 antiserum collected from a rabbit that was immunized with the proteins in peak M2 of the HPLC separation of flea saliva extract described in Example 3 of related PCT



Publication No. WO 96/11,271 (i.e., fspM2 proteins).  
Immunoscreening was performed as described in Example 12 of  
related PCT Publication No. WO 96/11,271.

A nucleotide sequence for another nfspM nucleic acid  
5 molecule named nfspM(E)<sub>1704</sub> is denoted as SEQ ID NO:26.  
Translation of SEQ ID NO:26 suggests that nucleic acid  
molecule nfspM(E)<sub>1704</sub> encodes a full-length fspM protein of  
about 461 amino acids, referred to herein as PfspM(E)<sub>461</sub>,  
assuming the first residue spans from about nucleotide 24  
10 through about nucleotide 26 of SEQ ID NO:26 and a stop  
codon spanning from about nucleotide 1407 through about  
nucleotide 1409 of SEQ ID NO:26. This open reading frame,  
excluding the stop codon, comprises nucleic acid molecule  
nfspM(E)<sub>1383</sub> of the present invention, the nucleic acid  
15 sequence of which is represented herein by SEQ ID NO:28.  
The amino acid sequence of PfspM(E)<sub>461</sub> is denoted SEQ ID  
NO:27. PfspM(E)<sub>461</sub> has a calculated molecular weight of  
about 54,139 daltons and calculated pI of about 7.00. A  
Genbank homology search revealed no significant homology  
20 between SEQ ID NO:26 or SEQ ID NO:27 and known nucleic acid  
sequences or known amino acid sequences, respectively.

A nucleotide sequence for another nfspM nucleic acid  
molecule named nfspM(F)<sub>1758</sub> is denoted as SEQ ID NO:29.  
Translation of SEQ ID NO:29 suggests that nucleic acid  
25 molecule nfspM(F)<sub>1758</sub> encodes a non-full-length fspM protein  
of about 586 amino acids, referred to herein as PfspM(F)<sub>586</sub>,

assuming an open reading frame having a start codon spanning from about nucleotide 1 through about nucleotide 3 of SEQ ID NO:29. The amino acid sequence of PfspM(F)<sub>586</sub> is denoted SEQ ID NO:30. PfspM(F)<sub>586</sub> has a calculated molecular weight of about 66,547 daltons and calculated pI of about 4.80. A Genbank homology search revealed no significant homology between SEQ ID NO:29 or SEQ ID NO:30 and known nucleic acid sequences or known amino acid sequences, respectively.

#### Example 4

This Example demonstrates the expression of a fspM protein in *E. Coli* cells.

Flea saliva protein PHIS-PfspM(D)<sub>90</sub> fusion protein was produced in the following manner. An about 305-bp DNA fragment, referred to herein as nfspM(D)<sub>305</sub>, was isolated from nfspM(D)<sub>293</sub> (denoted SEQ ID NO:31) subcloned into pBluescript plasmid by digesting the nfspM(D)-containing plasmid with *Bam*H1 and *Xho*I restriction endonucleases. The digestion product was gel purified and subcloned into expression vector pTrcHisB that had been digested with *Bam*H1 and *Xho*I, and dephosphorylated. The resultant recombinant molecule, referred to herein as pHis-nfspM(D)<sub>305</sub>, was transformed into *E. coli* HB101 competent cells (available from Gibco BRL, Gaithersburg, MD) to form recombinant cell *E. coli*:pHis-nfspM(D)<sub>305</sub>. The recombinant

cell was cultured and expression of nfspM<sub>305</sub> induced using conditions described in Example 11A of related PCT Publication No. WO 96/11,271. Immunoblot analysis of recombinant cell *E. coli*:pHis-nfspM(D)<sub>305</sub> lysates using a T7 tag monoclonal antibody (Novagen, Inc) directed against the fusion portion of the recombinant PHis-nfspM(D)<sub>305</sub> fusion protein identified a protein of the appropriate size, namely an about 15,851 kD protein.

#### Example 5

This example describes the isolation of nucleic acid sequences encoding at least a portion of flea saliva proteins fspN(C), fspN(D), fspN(E), fspN(F), fspN(G), fspN(H), fspN(I), fspN(J), fspN(K), fspN(L), fspN(M), fspN(N) and fspN(O).

#### A. Preparation of IgE enriched antiserum

Serum was obtained from the artificially sensitized dog CQQ2 (described in Example 8 of related PCT Publication No. WO 96/11,271). About 10 ml of antiserum was incubated with protein G-Sepharose (5 ml) over night at 4°C.

#### B. Immunoscreening with IgE enriched antiserum

About 2.4 ml of *Escherichia coli* (XL1 Blue, O.D.<sub>600</sub>=0.5) was incubated with  $6.48 \times 10^5$  pfu of phage from a flea salivary gland ZAP-cDNA library ( $1.8 \times 10^7$  pfu/ml), at 37°C for 15 min and plated in 12 Luria-Bertani (LB) medium agar plates (150 mm). The plates were incubated at 37°C over

night. Each plate was then overlaid with an IPTG (10mM) treated nitrocellulose filters for about 4 hours at 37°C. The filters were then removed and washed with TBST (20 mM Tris-HCl pH 7.5, 150 mM NaCl, 0.05% Tween-20). The filters were blocked with 5% dry milk in TBST for 2 hours at room temperature. Different filters were then incubated first with either IgE enriched CQQ2 antiserum or antiserum obtained from dogs infected with *Dirofilaria immitis* at 4°C, overnight, then with a monoclonal anti-canine IgE antibody (D-9; gift from the laboratory of Dr. D.J. DeBoer, School of Veterinary Medicine, University of Wisconsin, Madison, WI), and then with a donkey anti-mouse IgG antibody conjugated to horseradish peroxidase (available from Jackson ImmunoResearch, West Grove, PN) for 2 hours at room temperature at each step. All of the filters were washed with TBST (3 x 15 min/wash) between each incubation. All of the filters were then treated to a final wash in TBS. Immunocomplexed plaques were identified by immersing the filters into the developing solution (TMB Peroxidase Substrate/TMB Peroxidase Solution/TMB Membrane Enhancer from Kirkegaard & Perry Laboratories) at 1/1/0.1 volume ratio to produce a color reaction. Eighteen plaques were identified and further plaque purified under the same immunoscreening condition as described above.

C. nfspN(C)<sub>335</sub>, nfspN(D)<sub>390</sub> nfspN(E)<sub>265</sub> nfspN(F)<sub>228</sub>  
nfspN(G)<sub>339</sub>, nfspN(G)<sub>493</sub>,

Single plaque of purified clones were isolated and stored in SM phage buffer (50mM Tris, pH 7.4, 0.58% NaCl, 0.2% MgCl<sub>2</sub>·7H<sub>2</sub>O and 0.01% Gelatin). The *in vivo* excision of the pBluescript phagemid from each positive clone was prepared by using ExAssist™/SOLR™ system (Stratagene). The pBluescript plasmid was purified by plasmid midi kit (Qiagen), and denatured with NaOH (0.4 N) at 37°C for 15 min. The denatured plasmid was precipitated by ethanol and nucleic acid sequence obtained.

A nucleotide sequence for a nfspN nucleic acid molecule named nfspN(C)<sub>335</sub> is denoted as SEQ ID NO:32. A Genbank homology search revealed some similarity between SEQ ID NO:32 and ribosomal protein S6.

A nucleotide sequence for another nfspN nucleic acid molecule named nfspN(D)<sub>396</sub> is denoted as SEQ ID NO:33. A Genbank homology search revealed some similarity between SEQ ID NO:33 and erythropoietin.

A nucleotide sequence for another nfspN nucleic acid molecule named nfspN(E)<sub>285</sub> is denoted as SEQ ID NO:34. A Genbank homology search revealed some similarity between SEQ ID NO:34 and glutamic acid-rich protein or heat-shock protein, HSP81.

A nucleotide sequence for another nfspN nucleic acid molecule named nfspN(F)<sub>228</sub> is denoted as SEQ ID NO:35.

Nucleic acid sequence for portions of another nfspN nucleic acid molecule, denoted herein as nfspN(G), were

obtained. The nucleic acid molecule representing a 5' portion of nfspN(G) named nfspN(G)<sub>339</sub> is denoted as SEQ ID NO:36. Translation of SEQ ID NO:36 suggests that nucleic acid molecule nfspN(G)<sub>339</sub> encodes a non-full-length fspN(G) protein of about 113 amino acids, referred to herein as PfspN(G)<sub>113</sub>, assuming the first residue spans from about nucleotide 1 through about nucleotide 3 of SEQ ID NO:36. The amino acid sequence of PfspN(G)<sub>113</sub> is denoted SEQ ID NO:37.

The nucleic acid molecule representing a 3' portion of nfspN(G) named nfspN(G)<sub>493</sub> is denoted as SEQ ID NO:38. Translation of SEQ ID NO:38 suggests that nucleic acid molecule nfspN(G)<sub>493</sub> encodes a non-full-length fspN(G) protein of about 130 amino acids, referred to herein as PfspN(G)<sub>130</sub>, assuming the first residue spans from about nucleotide 1 through about nucleotide 3 of SEQ ID NO:38 and a stop codon spanning from about nucleotide 391 through about nucleotide 393 of SEQ ID NO:38. The amino acid sequence of PfspN(G)<sub>130</sub> is denoted SEQ ID NO:39. A Genbank homology search revealed some similarity between SEQ ID NO:36 and SEQ ID NO:38 and vitellogenin.

A nucleotide sequence for another nfspN nucleic acid molecule named nfspN(H)<sub>306</sub> is denoted as SEQ ID NO:40.

A nucleotide sequence for another nfspN nucleic acid molecule named nfspN(I)<sub>490</sub> is denoted as SEQ ID NO:41.

A nucleotide sequence for another nfspN nucleic acid molecule named nfspN(J)<sub>616</sub> is denoted as SEQ ID NO:42.

A nucleotide sequence for another nfspN nucleic acid molecule named nfspN(K)<sub>475</sub> is denoted as SEQ ID NO:43.

5 A nucleotide sequence for another nfspN nucleic acid molecule named nfspN(L)<sub>295</sub> is denoted as SEQ ID NO:44.

A nucleotide sequence for another nfspN nucleic acid molecule named nfspN(M)<sub>372</sub> is denoted as SEQ ID NO:45.

10 Nucleic acid sequence for portions of another nfspN nucleic acid molecule, denoted herein as nfspN(N), were obtained. The nucleic acid molecule representing a 5' portion of nfspN(N) named nfspN(N)<sub>252</sub> is denoted as SEQ ID NO:46. The nucleic acid molecule representing a 3' portion of nfspN(N) named nfspN(N)<sub>613</sub> is denoted as SEQ ID NO:47.

15 Nucleic acid sequence for portions of another nfspN nucleic acid molecule, denoted herein as nfspN(O), were obtained. The nucleic acid molecule representing a 5' portion of nfspN(O) named nfspN(O)<sub>538</sub> is denoted as SEQ ID NO:48. Translation of SEQ ID NO:48 suggests that nucleic acid molecule nfspN(O)<sub>538</sub> encodes a non-full-length fspN(O) protein of about 178 amino acids, referred to herein as PfspN(O)<sub>178</sub>, assuming the first residue spans from about nucleotide 1 through about nucleotide 3 of SEQ ID NO:48. The amino acid sequence of PfspN(N)<sub>178</sub> is denoted SEQ ID  
20  
25 NO:49.

The nucleic acid molecule representing a 3' portion of nfspN(O) named nfspN(O)<sub>432</sub> is denoted as SEQ ID NO:50. Translation of SEQ ID NO:50 suggests that nucleic acid molecule nfspN(O)<sub>432</sub> encodes a non-full-length fspN(O) protein of about 129 amino acids, referred to herein as PfspN(O)<sub>129</sub>, assuming the first residue spans from about nucleotide 1 through about nucleotide 3 of SEQ ID NO:50 and a stop codon spanning from about nucleotide 388 through about nucleotide 390 of SEQ ID NO:50. The amino acid sequence of PfspN(O)<sub>129</sub> is denoted SEQ ID NO:51.

#### Example 6

This example describes studies confirming the specificity of IgE enriched antiserum from CQQ2 to fspN protein.

Three different petri dishes (100 mm) were overlaid with 300 microliter per plate of *E. coli* (XL1 Blue, O.D.<sub>600</sub>=500). A drop (about 100 pfu/drop) of each of the eighteen isolated phage clones was dropped onto each plate (18 phage clones/plate). Using the methods described in Example 5 above, the plates were incubated, filter lifted and the filters immunoscreened with IgE enriched antiserum from CQQ2, antiserum from a *D. Immitis* infected dog and antiserum from rabbits injected with flea saliva product from peak N (as described in Example 3 of related PCT Publication No. WO 96/11,271).



The results of the experiment indicate that both the IgE enriched CQQ2 antiserum and the antiserum specific for peak N flea saliva product bind to the products of the purified phage clones significantly better than the antiserum from a *D. Immitis* infected dog.

#### Example 7

This example describes the isolation of nucleic acid molecules encoding a fspG flea saliva protein. This example also describes expression of a fspG protein by bacteria.

A DNA probe labeled with  $^{32}\text{P}$  comprising nucleotides from nfspG4<sub>610</sub> (described in Example 2) was used to screen a flea salivary gland cDNA library (described in Example 6 of related PCT Publication No. WO 96/11,706) using standard hybridization techniques. A clone was isolated having about a 595 nucleotide insert, referred to herein as nfspG5<sub>595</sub> having a nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:52. Translation of SEQ ID NO:52 suggests that nucleic acid molecule nfspG5<sub>595</sub> encodes a full-length flea salivary protein of about 90 amino acids, referred to herein as PfspG5<sub>90</sub>, having amino acid sequence SEQ ID NO:53, assuming an open reading frame in which the initiation codon spans from about nucleotide 46 through about nucleotide 48 of SEQ ID NO:52 and the termination codon spans from about nucleotide 316 through about nucleotide 318 of SEQ ID NO:52. The complement of

SEQ ID NO:52 is represented herein by SEQ ID NO:54. The coding region encoding PfspG5<sub>90</sub>, is represented by nucleic acid molecule nfspG5<sub>270</sub>, having a coding strand with the nucleic acid sequence represented by SEQ ID NO:55 and a complementary strand with nucleic acid sequence SEQ ID NO:57. The amino acid sequence of PfspG5<sub>90</sub> (i.e., SEQ ID NO:53) predicts that PfspG5<sub>90</sub> has an estimated molecular weight of about 9.6 kD and an estimated pI of about 9.28.

Analysis of SEQ ID NO:53 suggests the presence of a signal peptide encoded by a stretch of amino acids spanning from about amino acid 1 through about amino acid 19. The proposed mature protein, denoted herein as PfsG5<sub>71</sub>, contains about 71 amino acids which is represented herein as SEQ ID NO:59. The complement of SEQ ID NO:58 is represented by SEQ ID NO:60. The amino acid sequence of PfspG5<sub>71</sub> (i.e., SEQ ID NO:59) predicts that PfspG5<sub>71</sub> has an estimated molecular weight of about 7.48 kD, and an estimated pI of about 8.28.

Comparison of amino acid sequence SEQ ID NO:53 with amino acid sequences reported in GenBank indicates that SEQ ID NO:53 showed the most homology, i.e., about 38% identity between SEQ ID NO:53 and a *Ctenocephalides felis flea salivary protein FS-H precursor* (GenBank accession U63544). Comparison of nucleic acid sequence SEQ ID NO:52 with nucleic acid sequences reported in GenBank indicates

that SEQ ID NO:52 showed the most homology, i.e., about 63% identity between SEQ ID NO:52 and a *Ctenocephalides felis* flea salivary protein FS-H precursor gene (GenBank accession U63544).

5 Flea salivary protein PfspG5<sub>71</sub> was produced in the following manner. An about 213 bp nucleic acid molecule, referred to herein as nfspG5<sub>213</sub> (designed to encode an apparently mature flea salivary protein) was PCR amplified from nfspG5<sub>595</sub> using sense primer G7 having the nucleotide  
10 sequence 5' A GTG GAT CCG TCA AAA ATG GTC ACT G-3' (containing an *Bam*HI-site shown in bold; denoted SEQ ID NO:79) and anti-sense primer G8 having the nucleotide sequence 5' CC GGA ATT CGG TTA TTC GCA ATA ACA GT-3' (containing a *Eco*RI shown in bold; denoted SEQ ID NO:80).  
15 The resulting PCR product nfspG5<sub>213</sub> was digested with *Bam*HI and *Eco*RI restriction endonucleases, gel purified, and subcloned into expression vector lambdaP<sub>R</sub><sup>1</sup>/T<sup>2</sup>ori/S10HIS-RSET-A9, that had been digested with *Bam*HI and *Eco*RI and dephosphorylated. The resultant recombinant molecule,  
20 referred to herein as pCro-nfspG5<sub>213</sub>, was transformed into *E. coli* BL-21 competent cells (available from Novagen, Madison, WI) to form recombinant cell *E. coli*:pCro-nfspG5<sub>213</sub>. The recombinant cell was cultured and induced as described in Example 11A of related PCT Publication No. WO 96/11,271.  
25 Immunoblot analysis of the proteins using a T7 antibody

showed expression of an about 12 kD protein in the induced sample but not in the uninduced sample.

#### Example 8

5 This example describes the further sequencing of a nucleic acid sequence encoding a fspI flea saliva protein. This example also describes expression of a fspI protein by bacteria.

10 The nucleic acid molecule denoted nfspI<sub>573</sub> described in Example 6 of related PCT Publication No. WO 96/11,706 was further sequenced using standard nucleotide sequencing methods. A nucleic acid molecule was identified of about 1007 nucleotides, referred to herein as nfspI<sub>1007</sub>, the coding strand is denoted herein as SEQ ID NO:61. Translation of SEQ ID NO:61 suggests that SEQ ID NO:61 encodes a non-full-length flea salivary protein of about 155 amino acids, referred to herein as PfspI<sub>155</sub>, having amino acid sequence SEQ ID NO:62, assuming the first codon spans from about nucleotide 1 through about nucleotide 3 of SEQ ID NO:61 and the termination codon spans from about nucleotide 466 through about nucleotide 468 of SEQ ID NO:61. The complement of SEQ ID NO:61 is represented herein by SEQ ID NO:63.

25 Flea salivary protein PfspI<sub>158</sub> was produced in the following manner. An about 474-bp nucleic acid molecule, referred to herein as nfspI<sub>474</sub> (designed to encode an apparently mature flea salivary protein) was PCR amplified

from nfspI<sub>1007</sub> using sense primer I1 having the nucleotide sequence 5' GCG CGG ATC CGC ATA TGG AAG ACA TCT GGA AAG TTA ATA AAA AAT GTA CAT CAG-3' (containing an *Bam*HI-site shown in bold as well as nucleic acid sequence encoding three amino acids, Glu-Asp-Isoleucine, shown in italics; denoted SEQ ID NO:81) and anti-sense primer I2 having the nucleotide sequence 5' CCG **GAA** TTC TTA TTT ATT TTT TGG TCG ACA ATA ACA AAA GTT TCC-3' (containing a *Eco*RI shown in bold; denoted SEQ ID NO:82). The resulting PCR product nfspI<sub>474</sub>, which contained the nucleic acid sequences incorporated into primer I1 that encode three amino acids, was digested with *Bam*HI and *Eco*RI restriction endonucleases, gel purified, and subcloned into expression vector lambdaP<sub>R</sub>/T<sup>2</sup>ori/S10HIS-RSET-A9, that had been digested with *Bam*HI and *Xba*I and dephosphorylated. The resultant recombinant molecule, referred to herein as pCro-nfspI<sub>474</sub>, was transformed into *E. coli* BL-21 competent cells (available from Novagen, Madison, WI) to form recombinant cell *E. coli*:pCro-nfspI<sub>474</sub>. The recombinant cell was cultured and protein production resolved using the methods described in Example 11A of related PCT Publication No. WO 96/11,271. Immunoblot analysis of the proteins using a T7 antibody showed expression of an about 30 kD protein in the induced sample but not in the uninduced sample.

Example 9

This example describes the isolation of nucleic acid molecules encoding a fspN flea saliva protein.

A DNA probe comprising nucleotides from nfspN(B)<sub>612</sub> (SEQ ID NO:52 of related PCT Publication No. WO 96/11,706) was labeled with <sup>32</sup>P and used to screen the flea salivary gland cDNA library using standard hybridization techniques. A clone was isolated having about a 1205 nucleotide insert, referred to herein as nfspN5<sub>1205</sub> having a nucleic acid sequence of the coding strand which is denoted herein as SEQ ID NO:64. Translation of SEQ ID NO:64 suggests that nucleic acid molecule nfspN5<sub>1205</sub> encodes a non-full-length flea salivary protein of about 353 amino acids, referred to herein as PfspN5<sub>353</sub>, having amino acid sequence SEQ ID NO:65, assuming an open reading frame in which the initiation codon spans from about nucleotide 4 through about nucleotide 6 of SEQ ID NO:64 and the termination codon spans from about nucleotide 1060 through about nucleotide 1062 of SEQ ID NO:64. The complement of SEQ ID NO:64 is represented herein by SEQ ID NO:66. The coding region encoding PfspN5<sub>353</sub>, is represented by nucleic acid molecule nfspN5<sub>1059</sub>, having a coding strand with the nucleic acid sequence represented by SEQ ID NO:67 and a complementary strand with nucleic acid sequence SEQ ID NO:69. The amino acid sequence of PfspN5<sub>353</sub> (i.e., SEQ ID NO:65) predicts that

PfspN5<sub>353</sub> has an estimated molecular weight of about 39.7 kD and an estimated pI of about 9.45.

Comparison of amino acid sequence SEQ ID NO:65 with amino acid sequences reported in GenBank indicates that SEQ ID NO:65 showed the most homology, i.e., about 32% identity between SEQ ID NO:65 and a Human prostatic acid phosphatase precursor protein (GenBank accession P15309). A GenBank homology search revealed no significant homology between SEQ ID NO:64 and known nucleic acid sequences.

#### Example 10

This example describes the isolation of nucleic acid molecules encoding a fspN flea saliva protein identified using IgE antibodies isolated from a dog having clinical flea allergy dermatitis.

A pool of sera (referred to herein as Pool #4) was collected from numerous known to have clinic flea allergy dermatitis (FAD). Pool #4 sera was used to identify flea saliva antigens that bind specifically to IgE antibodies in the FAD dog sera as follows. Flea saliva extract was collected using the general methods described in Examples 1 and 2 of related PCT Publication No. WO 96/11,706, except a carboxymethyl cation exchange (CM) membrane (available from Schleicher and Scheull, Keene, NH) was used rather than a Durapore® membrane. In addition, flea saliva extract was eluted from the membrane by contacting the membrane in an extraction buffer of 2.5 M NaCl, 5%

isopropyl alcohol (IPA) and 20 mM Tris, pH 8.0. The membrane was eluted overnight at room temperature. The flea saliva extract was resolved by high pressure liquid chromatography (HPLC) using the method generally described in Example 2 of related PCT Publication No. WO 96/11,706. Proteins contained in the HPLC fractions were resolved on a 16% Tris-glycine SDS PAGE gel. Proteins on the gel were then blotted to an Immobilon P<sup>TM</sup> filter (available from Millipore Co., Bedford, MA) using standard Western Blot techniques. IgE antibodies bound to protein on the blot was then detected as follows. The blot was first incubated with about a 1:200 dilution of Pool #4 sera using standard antibody hybridization techniques, washed, and then incubated with about a 1:500 dilution of a 145 µg/milliliter solution of biotinylated human Fc R alpha chain protein using standard Western Blot techniques. Following washing, the blot was incubated with about a 1:5,000 dilution of streptavidin conjugated to alkaline phosphatase (available from Sigma, St. Louis, MO). About 10 milliliter of BCIP/NBT substrate (available from Gibco BRL, Gaithersburg, MD) was then added to the blot, incubated until visible bands appeared, at room temperature, and then the blot was rinsed in water to stop the reaction. Protein bands were detected in samples containing Fractions 34, 37, 38, 47, 49, 51, 52 and 53.



Amino (N-) terminal amino acid sequencing analysis was performed on protein contained in the about 40 kD protein band identified in the sample containing Fraction 52, using standard procedures known to those in the art (see, for example, Geisow et al., 1989, in *Protein Sequencing: A Practical Approach*, JBC Findlay and MJ Geisow (eds.), IRL Press, Oxford, England, pp. 85-98; Hewick et al., 1981, *J. Biol. Chem.*, Vol. 256, pp. 7990-7997). The N-terminal partial amino acid sequence of the protein was determined to be X Glu Leu Lys Phe Val Phe Val Met Val Lys Gly Pro Asp His Glu Ala Cys Asn Tyr Ala Gly Gly X Gln (denoted herein as SEQ ID NO:70; wherein "X" represents any amino acid residue).

Synthetic oligonucleotide primers were designed using SEQ ID NO:70 and used to isolate a nucleic acid molecule encoding SEQ ID NO:70 as follows. Sense primer 1 having the nucleotide sequence 5' AAA TTT GTA(T) TTT GTA(T) ATG GTA(T) AAA GGA(T) CCA(T) GAT CAT GAA GC -3' (denoted SEQ ID NO:83) was used in combination with the M13 forward universal standard primer 5' GTAAAACGACGGCCAGT 3' (denoted SEQ ID NO:84) to produce a PCR product from the a flea salivary gland cDNA library described above in Example 9. PCR amplification was conducted using standard techniques. The resulting PCR amplification product was a fragment of about 406 nucleotides, denoted herein as nfspN6<sub>406</sub>. The PCR product

was cloned into the InVitrogen, Corp., TA<sup>TM</sup> cloning vector (procedures provided by InVitrogen, Corp.) and subjected to DNA sequence analysis using standard techniques.

The nucleic acid sequence of the coding strand of nfspN6<sub>406</sub> is denoted herein as SEQ ID NO:71. Translation of SEQ ID NO:71 suggests that nucleic acid molecule nfspN6<sub>406</sub> encodes a non-full-length flea salivary protein of about 135 amino acids, referred to herein as PfspN6<sub>135</sub>, having amino acid sequence SEQ ID NO:72, assuming the first codon spans from about nucleotide 1 through about nucleotide 3 of SEQ ID NO:71 and the last codon spans from about nucleotide 403 through about nucleotide 405 of SEQ ID NO:71. The complement of SEQ ID NO:71 is represented herein by SEQ ID NO:73.

A GenBank homology search revealed no significant homology between amino acid sequence SEQ ID NO:72 and nucleic acid sequence SEQ ID NO:71 and known amino acid sequences or nucleic acid sequences, respectively.

#### Example 11

This example describes the isolation of nucleic acid molecules encoding a fspJ flea saliva protein.

Degenerate oligonucleotide primers were designed from the amino acid sequence deduced for fspJ (described in Example 4 of related PCT Publication No. WO 96/11,706) and were used to isolate a fspJ nucleic acid molecule as follows. Two synthetic oligonucleotides were synthesized

that corresponded to the region of fspJ spanning from about residues 7 through about 26 of SEQ ID NO:8 of related PCT Publication No. WO 96/11,706. Primer 1, a "sense" primer corresponding to amino acid residues from about residue 7 to about 16 of SEQ ID NO:8 of related PCT Publication No. WO 96/11,706, has the nucleotide sequence 5' CAT GAA CCA(T) GGA(T) AAT ACA(T) CGA(T) AAA(G) ATA(C/T) A(C)G 3' (denoted herein as SEQ ID NO:84). Primer 2, a "sense" primer corresponding to amino acid residues from about residue 17 through about 26 of SEQ ID NO:8 of related PCT Publication No. WO 96/11,706, has the nucleic acid sequence 5' GAA GTA(T) ATG GAC(T) AAA TTA(G) AGA(G) CAA(G) GC -3' (denoted herein as SEQ ID NO:86).

PCR amplification of fragments from the flea salivary gland cDNA library described above in Example 9 was conducted using standard techniques. PCR amplification products were generated using a combination of Primer 1 and M13 primer (denoted SEQ ID NO:85). The resultant PCR products were used for a nested PCR amplification using Primer 2 and the T7 standard primer 5' GTA ATA CGA CTC ACT ATA TAG GGC 3' (denoted SEQ ID NO:88). The resultant PCR product, a fragment of about 420 nucleotides, denoted herein as nfspJ<sub>420</sub>. The PCR product was cloned into the InVitrogen, Corp., TA<sup>TM</sup> cloning vector (procedures provided by InVitrogen, Corp.) and subjected to DNA sequence analysis using standard techniques.

The nucleic acid sequence of the coding strand of nfspJ<sub>420</sub> is denoted herein as SEQ ID NO:74. Translation of SEQ ID NO:74 suggests that nucleic acid molecule nfspJ<sub>420</sub> encodes a non-full-length flea salivary protein of about 72 amino acids, referred to herein as PfspJ<sub>72</sub>, having amino acid sequence SEQ ID NO:75, assuming the first codon spans from about nucleotide 1 through about nucleotide 3 of SEQ ID NO:74 and the last codon spans from about nucleotide 214 through about nucleotide 216 of SEQ ID NO:74. The complement of SEQ ID NO:74 is represented herein by SEQ ID NO:76.

A GenBank homology search revealed no significant homology between amino acid sequence SEQ ID NO:75 and nucleic acid sequence SEQ ID NO:74 and known amino acid sequences or nucleic acid sequences, respectively.

#### Example 12

This example describes the amino acid sequence analysis of an isolated and HPLC purified fspN7 flea saliva protein.

Fractions of flea saliva proteins described above in Example 10 were tested for the ability to stimulate T cell clones that respond specifically to the flea saliva extract described in Example 10 (FS-specific T cells). T cell activation were performed using standard methods such as those described in *Current Protocols in Immunology*, Vol. 1, Chapter 3 [3.13.2], ed. J.E. Coligan et al., pub. Wiley

Interscience, 1993. Briefly, about  $10^4$  FS-1-specific T cells (clone CP02-7; isolated from dog CP02 described in Example 8 of related PCT Patent Publication No. WO 96/11,271) were added to individual wells of a 96 well tissue culture plate, in the presence of about  $2 \times 10^4$  autologous antigen presenting cells (isolated by ficoll gradient from dog CP02) and about 100 units/milliliter of recombinant human interleukin-2 (Proleukin®; available from Chiron Inc., Emeryville, CA). About 1 microliter of each fraction of protein resolved by HPLC was to added to each well in triplicate. The cells were incubated for about 4 to about 6 days. About 16 hours prior to harvesting, about 1  $\mu$ Ci of tritiated thymidine (available from Amersham Inc., Arlington Heights, IL) was added to each well. The cells were then harvested and the amount of tritium incorporated into the cellular protein was determined. The results indicated that protein contained in a HPLC fraction containing fspN protein (Fraction 51) stimulated the FS-specific T cells.

Amino (N-) terminal amino acid sequencing analysis was performed on protein contained in Fraction 51 using standard procedures known to those in the art (see, for example, Geisow et al., *ibid.*; Hewick et al., 1981, *ibid.*). The N-terminal partial amino acid sequence of the band was determined to be Asn Asp Lys Leu Gln Phe Val Phe Val Met

Ala Arg Gly Pro Asp His Glu Ala Cys Asn Tyr Pro Gly Gly Pro  
(denoted herein as SEQ ID NO:78).

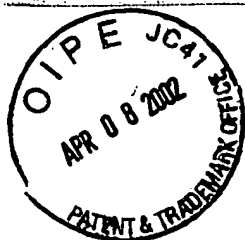
Example 13

5 This example describes the amino acid sequence  
analysis of an isolated and HPLC purified fspM2 flea saliva  
protein.

10 Proteins contained within Fraction 47 described above  
in Example 10 were resolved on a 16% Tris-glycine SDS PAGE  
gel. A major band at about 34 kD was identified. Amino  
(N-) terminal amino acid sequencing analysis was performed  
on protein contained in the about 34 kD using standard  
procedures known to those in the art (see, for example,  
Geisow et al., *ibid.*; Hewick et al., 1981, *ibid.*). The N-  
15 terminal partial amino acid sequence of the band was  
determined to be Tyr Phe Asn Lys leu Val Gln Ser Trp Thr  
Glu Pro Met Val Phe Lys Tyr Pro Tyr (denoted herein as SEQ  
ID NO:87).

While various embodiments of the present invention have been described in detail, it is apparent that modifications and adaptations of those embodiments will occur to those skilled in the art. It is to be expressly understood, however, that such modifications and adaptations are within the scope of the present invention, as set forth in the following claims.

1004764 040902



## SEQUENCE LISTING

The following Sequence Listing is submitted pursuant to 37 CFR §1.821. A copy in computer readable form is also submitted herewith.

5 Applicants assert pursuant to 37 CFR §1.821(f) that the content of the paper and computer readable copies of SEQ ID NO:1 through SEQ ID NO:88 submitted herewith are the same.

## (1) GENERAL INFORMATION:

(i) APPLICANT: Frank, Glenn R.  
Wu Hunter, Shirley  
Wallenfels, Lynda

(ii) TITLE OF INVENTION: NOVEL ECTOPARASITE SALIVA PROTEINS AND APPARATUS TO COLLECT SUCH PROTEINS

(iii) NUMBER OF SEQUENCES: 88

## (iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: SHERIDAN ROSS P.C.  
(B) STREET: 1700 LINCOLN ST., SUITE 3500  
(C) CITY: DENVER  
(D) STATE: CO  
(E) COUNTRY: U.S.A.  
(F) ZIP: 80203

## (v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

## (vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:  
(B) FILING DATE:  
(C) CLASSIFICATION:

## (viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Connell, Gary J.  
(B) REGISTRATION NUMBER: 32,020  
(C) REFERENCE/DOCKET NUMBER: 2618-17-C4

## (ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 303/863-9700  
(B) TELEFAX: 303/863-0223

## (2) INFORMATION FOR SEQ ID NO:1:



- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 26 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Met Arg Gly Asn His Val Phe Leu Glu Asp Gly Met Ala Asp Met Thr  
 1 5 10 15

Gly Gly Gln Gln Met Gly Arg Asp Leu Tyr  
 20 25

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 12 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

- (A) NAME/KEY: Xaa = Tyr or Asp  
 (B) LOCATION: 5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Lys Tyr Arg Asn Xaa Xaa Thr Asn Asp Pro Gln Tyr  
 1 5 10

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 27 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Glu Ile Lys Arg Asn Asp Arg Glu Pro Gly Asn Leu Ser Lys Ile Arg  
 1 5 10 15

Thr Val Met Asp Lys Val Ile Lys Gln Thr Gln  
 20 25

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 23 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY: Xaa = Ala or His  
(B) LOCATION: 8

(ix) FEATURE:

(A) NAME/KEY: Xaa = Ala or His<sup>t</sup>  
(B) LOCATION: 9

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Leu Lys Asp Asn Asp Ile Tyr Xaa Xaa Arg Asp Ile Asn Glu Ile Leu  
1 5 10 15

Arg Val Leu Asp Pro Ser Lys  
20

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Asn Tyr Gly Arg Val Gln Ile Glu Asp Tyr Thr Xaa Ser Asn His Lys  
1 5 10 15

Asp Xaa Glu Glu Lys Asp Gln Ile Asn Gly Leu  
20 25

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Lys Tyr Arg Asn Xaa Tyr Thr Asn Asp Pro Gln Leu Lys Leu Leu Asp  
1 5 10 15

Glu Gly

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Tyr Phe Asn Asp Gln Ile Lys Ser Val Met Glu Pro Xaa Val Phe Lys  
 1 5 10 15

Tyr Pro Xaa Ala Xaa Leu  
 20

5

## (2) INFORMATION FOR SEQ ID NO:8:

10

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 20 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

15

- (ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:

20

- (A) NAME/KEY: misc\_feature  
 (B) LOCATION: 1..20  
 (D) OTHER INFORMATION: /label= primer

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

25

TGRTTTCCWA TRAARTCTTC

20

## (2) INFORMATION FOR SEQ ID NO:9:

30

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 225 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

35

- (ii) MOLECULE TYPE: DNA (genomic)

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

40

GAATTCGGCA CGAGTGAAAT TCAATATTTT GTTTTACATT AAATTTTTC AATTCGATAT 60

GAAATTTTTA CTGGCAATTT GCGTGGTTGTG TGTTTATTA AATCAAGTAT CTATGTCAAA 120

45

AATGGTCACT GAAAAGTGTA AGTCAGGTGG AAATAATCCA AGTACAGAAG AGGTGTCAAT 180

ACCATCTGGG AAGCTTACTA TTGAAGATTT TTGTATTGGA AATCA 225

50

## (2) INFORMATION FOR SEQ ID NO:10:

55

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 15 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

60

- (ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:

65

- (A) NAME/KEY: misc\_feature  
 (B) LOCATION: 1..15  
 (D) OTHER INFORMATION: /label= primer

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

AATTCGGCAC GAGTG

15

## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 565 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 45..314

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

|    |   |     |
|----|---|-----|
| 20 | TGAAATTCAA TATTTTGTTC TACATTAAAT TTTTCAAATT CGAT ATG AAA TTT TTA  | 56  |
|    | Met Lys Phe Leu   |     |
|    | 1   |     |
| 25 | CTG GCA ATT TGC GTG TTG TGT GTT TTA TTA AAT CAA GTA TCT ATG TCA   | 104 |
|    | Leu Ala Ile Cys Val Leu Cys Val Leu Leu Asn Gln Val Ser Met Ser   |     |
|    | 5 10 15 20  |     |
| 30 | AAA ATG GTC ACT GAA AAG TGT AAG TCA GGT GGA AAT AAT CCA AGT ACA   | 152 |
|    | Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn Asn Pro Ser Thr   |     |
|    | 25 30 35  |     |
| 35 | GAA GAG GTG TCA ATA CCA TCT GGG AAG CTT ACT ATT GAA GAT TTT TGT   | 200 |
|    | Glu Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile Glu Asp Phe Cys   |     |
|    | 40 45 50  |     |
| 40 | ATT GGA AAT CAT CAA AGT TGC AAA ATA TTT TAC AAA AGT CAA TGT GGA   | 248 |
|    | Ile Gly Asn His Gln Ser Cys Lys Ile Phe Tyr Lys Ser Gln Cys Gly   |     |
|    | 55 60 65  |     |
| 45 | TTT GGA GGT GGT GCT TGT GGA AAC GGT GGT TCA ACA CGA CCA AAT CAA   | 296 |
|    | Phe Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr Arg Pro Asn Gln       |     |
|    | 70 75 80  |     |
| 50 | AAA CAC TGT TAT TGC GAA TAACCATATT CCGGATGAAA GACCAAATG           | 344 |
|    | Lys His Cys Tyr Cys Glu   |     |
|    | 85 90   |     |
| 55 | ATATAAATTA CTAAAATTAT GCTAGATAGC AATCATAAAA TTTTGAAGTT TTCAATGATC | 404 |
|    | CTAACATGTT TTGCCTCCAA TTTATTTTAA CAGCAAATTG CTGGAACCTA CCGTACCGTA | 464 |
|    | ACTAAATGTT CAAGAAATAC TGAATGTTTA CAAATAGATT ATTATAAATA TTGTAACATT | 524 |
|    | GTCTAATATT TATAAGAATT ATATAAACTG AATTGCAAAA A                     | 565 |

## (2) INFORMATION FOR SEQ ID NO:12:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 90 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Lys Phe Leu Leu Ala Ile Cys Val Leu Cys Val Leu Leu Asn Gln  
 1 5 10 15  
 Val Ser Met Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn  
 20 25 30  
 Asn Pro Ser Thr Glu Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile  
 35 40 45  
 Glu Asp Phe Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Tyr Lys  
 50 55 60  
 Ser Gln Cys Gly Phe Gly Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr  
 65 70 75 80  
 Arg Pro Asn Gln Lys His Cys Tyr Cys Glu  
 85 90

## (2) INFORMATION FOR SEQ ID NO:13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 270 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 1..270

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

ATG AAA TTT TTA CTG GCA ATT TGC GTG TTG TGT GTT TTA TTA AAT CAA 48  
 Met Lys Phe Leu Leu Ala Ile Cys Val Leu Cys Val Leu Leu Asn Gln  
 1 5 10 15  
 GTA TCT ATG TCA AAA ATG GTC ACT GAA AAG TGT AAG TCA GGT GGA AAT 96  
 Val Ser Met Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn  
 20 25 30  
 AAT CCA AGT ACA GAA GAG GTG TCA ATA CCA TCT GGG AAG CTT ACT ATT 144  
 Asn Pro Ser Thr Glu Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile  
 35 40 45  
 GAA GAT TTT TGT ATT GGA AAT CAT CAA AGT TGC AAA ATA TTT TAC AAA 192  
 Glu Asp Phe Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Tyr Lys  
 50 55 60  
 AGT CAA TGT GGA TTT GGA GGT GGT GCT TGT GGA AAC GGT GGT TCA ACA 240  
 Ser Gln Cys Gly Phe Gly Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr  
 65 70 75 80  
 CGA CCA AAT CAA AAA CAC TGT TAT TGC GAA 270  
 Arg Pro Asn Gln Lys His Cys Tyr Cys Glu  
 85 90

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 90 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

5 Met Lys Phe Leu Leu Ala Ile Cys Val Leu Cys Val Leu Leu Asn Gln  
 1 5 10 15  
 Val Ser Met Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn  
 20 25 30  
 10 Asn Pro Ser Thr Glu Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile  
 35 40 45  
 Glu Asp Phe Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Tyr Lys  
 50 55 60  
 15 Ser Gln Cys Gly Phe Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr  
 65 70 75 80  
 Arg Pro Asn Gln Lys His Cys Tyr Cys Glu  
 85 90

## (2) INFORMATION FOR SEQ ID NO:15:

## (i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 26 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE:

- 30 (A) NAME/KEY: misc feature  
 35 (B) LOCATION: 1..26  
 (D) OTHER INFORMATION: /label= primer

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

40 AGTGGATCCG TCAAAAATGG TCACTG

26

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- 45 (A) LENGTH: 28 base pairs  
 (B) TYPE: nucleic acid  
 50 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE:

- 55 (A) NAME/KEY: misc feature  
 (B) LOCATION: 1..28  
 (D) OTHER INFORMATION: /label= primer

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

60 CCGGAATTCTG GTTATTCGCA ATAACAGT

28

## (2) INFORMATION FOR SEQ ID NO:17:

## (i) SEQUENCE CHARACTERISTICS:

- 65 (A) LENGTH: 897 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 97..568

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```

10  CCGAAATCTC CTATCACAGT GTACGGAGTG TAAATATTG TTGAAGTATT TTGAAATTTA      60
    TTAATTTATT CGAAAAGGAG ATTCATTAA ATAAAA ATG GTT TAC GAA AGT GAC      114
                                   Met Val Tyr Glu Ser Asp
15                                   1       5
    TTT TAC ACG ACC CGT CGG CCC TAC AGT CGT CCG GCT TTG TCT TCA TAC      162
    Phe Tyr Thr Thr Arg Arg Pro Tyr Ser Arg Pro Ala Leu Ser Ser Tyr
                                   10       15       20
20  TCC GTA ACG GCA CGT CCA GAG CCG GTT CCT TGG GAC AAA TTG CCG TTC      210
    Ser Val Thr Ala Arg Pro Glu Pro Val Pro Trp Asp Lys Leu Pro Phe
                                   25       30       35
25  GTC CCC CGT CCA AGT TTG GTA GCA GAT CCC ATA ACA GCA TTT TGC AAG      258
    Val Pro Arg Pro Ser Leu Val Ala Asp Pro Ile Thr Ala Phe Cys Lys
                                   40       45       50
30  CGA AAA CCT CGC CGA GAA GAA GTT GTT CAA AAA GAG TCC ATT GTT CGA      306
    Arg Lys Pro Arg Arg Glu Glu Val Val Gln Lys Glu Ser Ile Val Arg
                                   55       60       65
35  AGG ATC AAT TCT GCA GGA ATT AAA CCC AGC CAG AGA GTT TTA TCG GCT      354
    Arg Ile Asn Ser Ala Gly Ile Lys Pro Ser Gln Arg Val Leu Ser Ala
                                   75       80       85
40  CCA ATA AGA GAA TAC GAA TCC CCA AGG GAC CAG ACC AGG CGT AAA GTT      402
    Pro Ile Arg Glu Tyr Glu Ser Pro Arg Asp Gln Thr Arg Arg Lys Val
                                   90       95       100
45  TTG GAA AGC GTC AGA AGA CAA GAA GCT TTT CTG AAC CAA GGA GGA ATT      450
    Leu Glu Ser Val Arg Arg Gln Glu Ala Phe Leu Asn Gln Gly Gly Ile
                                   105       110       115
50  TGT CCA TTG ACC ACC AGA AAT GAT GAC ATG GAT AGA CTT CTA CCC CGT      498
    Cys Pro Leu Thr Thr Arg Asn Asp Asp Met Asp Arg Leu Leu Pro Arg
                                   120       125       130
55  CTC CAC AGT TCA CAC ACA ACA CCT TCT GCG GAT AGG AAA GTT TTG TTG      546
    Leu His Ser Ser His Thr Thr Pro Ser Ala Asp Arg Lys Val Leu Leu
                                   135       140       145       150
60  ACC ACT TTT CAC AGA AGA TAC T GATTAAAAAT GAAAGTTAAG AAATTTGTTG      598
    Thr Thr Phe His Arg Arg Tyr
                                   155
    AAGTCATGTG GTGTTTTTTA TACATTCTTT ATTAATCGAT ATTCCTAACG AACGATACGA      658
65  TAACTTTTCG TAACTTTTTT TGGTTAATTT TGACAAAATA TGCATTGCA AGCATAACAT      718
    TCATTTTCAG GGCAAACGCT TTCTGATGAT TATCTTGTTA AAAGTGTGGA AACAAGCGTA      778
    GTGTTAACAA ATGCATTGCT TGTTTGGATT ATTTATTTAT CTATTATATA TTCCATATTG      838
65  TATTGTAGGT GGTGTA CTG GTATTACTAA TACACGTACT TTGTGAAAAA AAAAAAAAAA      897

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(2) INFORMATION FOR SEQ ID NO:18:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 157 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

5

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

10 Met Val Tyr Glu Ser Asp Phe Tyr Thr Thr Arg Arg Pro Tyr Ser Arg  
     1                    5                    10                    15  
 Pro Ala Leu Ser Ser Tyr Ser Val Thr Ala Arg Pro Glu Pro Val Pro  
                     20                    25                    30  
 15 Trp Asp Lys Leu Pro Phe Val Pro Arg Pro Ser Leu Val Ala Asp Pro  
                     35                    40                    45  
 20 Ile Thr Ala Phe Cys Lys Arg Lys Pro Arg Arg Glu Glu Val Val Gln  
                     50                    55                    60  
 Lys Glu Ser Ile Val Arg Arg Ile Asn Ser Ala Gly Ile Lys Pro Ser  
                     65                    70                    75                    80  
 25 Gln Arg Val Leu Ser Ala Pro Ile Arg Glu Tyr Glu Ser Pro Arg Asp  
                     85                    90                    95  
 Gln Thr Arg Arg Lys Val Leu Glu Ser Val Arg Arg Gln Glu Ala Phe  
                     100                    105                    110  
 30 Leu Asn Gln Gly Gly Ile Cys Pro Leu Thr Thr Arg Asn Asp Asp Met  
                     115                    120                    125  
 35 Asp Arg Leu Leu Pro Arg Leu His Ser Ser His Thr Thr Pro Ser Ala  
                     130                    135                    140  
 Asp Arg Lys Val Leu Leu Thr Thr Phe His Arg Arg Tyr  
                     145                    150                    155

## (2) INFORMATION FOR SEQ ID NO:19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 471 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

45

## (ii) MOLECULE TYPE: cDNA

50

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

ATGGTTTACG AAGTGACTT TTACACGACC CGTCGGCCCT ACAGTCGTCC GGCTTTGTCT 60  
 55 TCATACTCCG TAACGGCAGC TCCAGAGCCG GTTCCTTGGG ACAAATTGCC GTTCGTCCCC 120  
 CGTCCAAGTT TGGTAGCAGA TCCATAACA GCATTTTGCA AGCGAAAACC TCGCCGAGAA 180  
 60 GAAGTTGTTC AAAAAGAGTC CATTGTTTGA AGGATCAATT CTGCAGGAAT TAAACCCAGC 240  
 CAGAGAGTTT TATCGGCTCC AATAAGAGAA TACGAATCCC CAAGGGACCA GACCAGGCGT 300  
 AAAGTTTGG AAAGCGTCAG AAGACAAGAA GCTTTTCTGA ACCAAGGAGG AATTTGTCCA 360  
 65 TTGACCACCA GAAATGATGA CATGGATAGA CTCTACCCC GTCTCCACAG TTCACACACA 420  
 ACACCTTCTG CGGATAGGAA AGTTTTGTTG ACCACTTTTC ACAGAAGATA C 471



## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2706 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 5..2706

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GCGG ATG AAG AGC ATC GAG GCT TAT ACA AAC AGA TAT GAA ATC ATA GCT 49  
 Met Lys Ser Ile Glu Ala Tyr Thr Asn Arg Tyr Glu Ile Ile Ala  
 1 5 10 15

TCT GAA ATA GTT AAT CTT CGA ATG AAA CCA GAT GAT TTT AAT TTA ATA 97  
 Ser Glu Ile Val Asn Leu Arg Met Lys Pro Asp Asp Phe Asn Leu Ile  
 20 25 30

AAA GTT ATT GGT CGA GGA GCA TTT GGT GAA GTA CAG TTA GTG CGA CAC 145  
 Lys Val Ile Gly Arg Gly Ala Phe Gly Glu Val Gln Leu Val Arg His  
 35 40 45

AAA TCA ACT GCA CAA GTT TTT GCT ATG AAA CGC CTA TCA AAA TTT GAA 193  
 Lys Ser Thr Ala Gln Val Phe Ala Met Lys Arg Leu Ser Lys Phe Glu  
 50 55 60

ATG ATT AAG AGA CCA GAC TCT GCA TTT TTT TGG GAA GAA CGT CAT ATA 241  
 Met Ile Lys Arg Pro Asp Ser Ala Phe Phe Trp Glu Glu Arg His Ile  
 65 70 75

ATG GCT CAT GCA AAA TCA GAA TGG ATT GTA CAA TTA CAT TTT GCT TTT 289  
 Met Ala His Ala Lys Ser Glu Trp Ile Val Gln Leu His Phe Ala Phe  
 80 85 90 95

CAA GAT CAA AAA TAT CTT TAT ATG GTC ATG GAT TAT ATG CCG GGG GGT 337  
 Gln Asp Gln Lys Tyr Leu Tyr Met Val Met Asp Tyr Met Pro Gly Gly  
 100 105 110

GAC TTG GTG AGT CTT ATG TCC GAT TAT GAA ATT CCA GAA AAA TGG GCA 385  
 Asp Leu Val Ser Leu Met Ser Asp Tyr Glu Ile Pro Glu Lys Trp Ala  
 115 120 125

ATG TTC TAT ACA ATG GAA GTG GTG CTA GCA CTT GAT ACA ATT CAC TCC 433  
 Met Phe Tyr Thr Met Glu Val Val Leu Ala Leu Asp Thr Ile His Ser  
 130 135 140

ATG GGA TTT GTA CAT CGT GAT GTT AAA CCT GAT AAT ATG CTT CTA GAC 481  
 Met Gly Phe Val His Arg Asp Val Lys Pro Asp Asn Met Leu Leu Asp  
 145 150 155

AAA TAT GGT CAT TTA AAG TTA GCT GAC TTT GGA ACC TGT ATG AAA ATG 529  
 Lys Tyr Gly His Leu Lys Leu Ala Asp Phe Gly Thr Cys Met Lys Met  
 160 165 170 175

GAT ACA GAT GGT TTG GTA CGT TCT AAT AAT GCT GTT GGA ACG CCT GAT 577  
 Asp Thr Asp Gly Leu Val Arg Ser Asn Asn Ala Val Gly Thr Pro Asp  
 180 185 190

TAC ATT TCT CCC GAA GTT TTG CAG TCC CAA GGT GGT GAA GGA GTT TAC 625  
 Tyr Ile Ser Pro Glu Val Leu Gln Ser Gln Gly Gly Glu Gly Val Tyr  
 195 200 205

|    |   |      |
|----|---|------|
|    | GGT CGT GAA TGC GAT TGG TGG TCT GTG GGA ATT TTT TTG TAT GAA ATG | 673  |
|    | Gly Arg Glu Cys Asp Trp Trp Ser Val Gly Ile Phe Leu Tyr Glu Met |      |
|    | 210 215 220   |      |
| 5  | TTA TTT GGA GAA ACA CCT TTT TAT GCA GAC AGT TTG GTT GGA ACT TAC | 721  |
|    | Leu Phe Gly Glu Thr Pro Phe Tyr Ala Asp Ser Leu Val Gly Thr Tyr |      |
|    | 225 230 235   |      |
| 10 | AGT AAA ATT ATG GAT CAC AGA AAC TCA TTA ACT TTT CCT CCA GAA GTG | 769  |
|    | Ser Lys Ile Met Asp His Arg Asn Ser Leu Thr Phe Pro Pro Glu Val |      |
|    | 240 245 250 255   |      |
| 15 | GAA ATA AGC CAA TAT GCC CGA TCT TTG ATA CAA GGA TTT TTA ACA GAC | 817  |
|    | Glu Ile Ser Gln Tyr Ala Arg Ser Leu Ile Gln Gly Phe Leu Thr Asp |      |
|    | 260 265 270   |      |
| 20 | AGA ACA CAG CGT TTA GGC AGA AAT GAA GTG GAA GAA ATT AAA CGA CAT | 865  |
|    | Arg Thr Gln Arg Leu Gly Arg Asn Glu Val Glu Glu Ile Lys Arg His |      |
|    | 275 280 285   |      |
| 25 | CCA TTT TTC ATA AAT GAT CAA TGG ACT TTT GAC AAT TTA AGA GAC TCT | 913  |
|    | Pro Phe Phe Ile Asn Asp Gln Trp Thr Phe Asp Asn Leu Arg Asp Ser |      |
|    | 290 295 300   |      |
| 30 | GCC CCA CCT GTA GTG CCA GAG CTG AGT GGT GAT GAT GAT ACA AGG AAC | 961  |
|    | Ala Pro Pro Val Val Pro Glu Leu Ser Gly Asp Asp Thr Arg Asn     |      |
|    | 305 310 315   |      |
| 35 | TTT GAT GAT ATT GAA CGT GAT GAA ACA CCT GAA GAG AAT TTT CCT ATA | 1009 |
|    | Phe Asp Asp Ile Glu Arg Asp Glu Thr Pro Glu Glu Asn Phe Pro Ile |      |
|    | 320 325 330 335   |      |
| 40 | CCA AAA ACT TTT GCT GGT AAT CAT CTG CCA TTT GTT GGA TTC ACA TAT | 1057 |
|    | Pro Lys Thr Phe Ala Gly Asn His Leu Pro Phe Val Gly Phe Thr Tyr |      |
|    | 340 345 350   |      |
| 45 | AAT GGT GAT TAC CAA TTA TTA ACA AAT GGA GGT GTT AGA AAT AGT GAT | 1105 |
|    | Asn Gly Asp Tyr Gln Leu Leu Thr Asn Gly Gly Val Arg Asn Ser Asp |      |
|    | 355 360 365   |      |
| 50 | ATG GTT GAT ACA AAA TTA AAC AAC ATT TGT GTT TCA AGT AAG GAT GAT | 1153 |
|    | Met Val Asp Thr Lys Leu Asn Asn Ile Cys Val Ser Ser Lys Asp Asp |      |
|    | 370 375 380   |      |
| 55 | GTG TTA AAT TTA CAA AAT TTA TTA GAA CAA GAG AAA GGT AAC AGT GAA | 1201 |
|    | Val Leu Asn Leu Gln Asn Leu Leu Glu Gln Glu Lys Gly Asn Ser Glu |      |
|    | 385 390 395   |      |
| 60 | AAT TTG AAA ACA AAC ACC CAA TTA TTA AGT AAT AAA TTA GAT GAA CTA | 1249 |
|    | Asn Leu Lys Thr Asn Thr Gln Leu Leu Ser Asn Lys Leu Asp Glu Leu |      |
|    | 400 405 410 415   |      |
| 65 | GGT CAG AGA GAA TGT GAA TTA AGG AAT CAG GCT GGA GAT TAT GAG AAA | 1297 |
|    | Gly Gln Arg Glu Cys Glu Leu Arg Asn Gln Ala Gly Asp Tyr Glu Lys |      |
|    | 420 425 430   |      |
| 70 | GAA TTG ACT AAA TTC AAA TTA TCG TGC AAA GAA TTA CAA CGT AAG GCA | 1345 |
|    | Glu Leu Thr Lys Phe Lys Leu Ser Cys Lys Glu Leu Gln Arg Lys Ala |      |
|    | 435 440 445   |      |
| 75 | GAA TTT GAG AAT GAA TTA CGG CGT AAA ACT GAG TCC TTA CTA GTT GAA | 1393 |
|    | Glu Phe Glu Asn Glu Leu Arg Arg Lys Thr Glu Ser Leu Leu Val Glu |      |
|    | 450 455 460   |      |
| 80 | ACA AAG AAA AGA CTA GAC GAA GAG CAG AAT AAA AGA ACT AGA GAA ATG | 1441 |
|    | Thr Lys Lys Arg Leu Asp Glu Glu Gln Asn Lys Arg Thr Arg Glu Met |      |
|    | 465 470 475   |      |
| 85 | AAT AAT AAT CAA CAG CAC AAT GAC AAA ATA AAT ATG TTA GAA AAA CAA | 1489 |

|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Asn | Asn | Asn | Gln | Gln | His | Asn | Asp | Lys | Ile | Asn | Met | Leu | Glu | Lys | Gln |      |
|    | 480 |     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |      |
| 5  | ATT | AAT | GAT | TTA | CAA | GAA | AAA | TTG | AAA | GGT | GAA | TTA | GAG | CAC | AAT | CAG | 1537 |
|    | Ile | Asn | Asp | Leu | Gln | Glu | Lys | Leu | Lys | Gly | Glu | Leu | Glu | His | Asn | Gln |      |
|    |     |     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |      |
| 10 | AAA | TTA | AAG | AAG | CAA | GCT | GTT | GAG | CTT | AGA | GTT | GCT | CAG | TCT | GCT | ACT | 1585 |
|    | Lys | Leu | Lys | Lys | Gln | Ala | Val | Glu | Leu | Arg | Val | Ala | Gln | Ser | Ala | Thr |      |
|    |     |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |      |
| 15 | GAA | CAA | CTG | AAT | AAT | GAA | TTA | CAG | GAA | ACT | ATG | CAG | GGT | TTA | CAA | ACA | 1633 |
|    | Glu | Gln | Leu | Asn | Asn | Glu | Leu | Gln | Glu | Thr | Met | Gln | Gly | Leu | Gln | Thr |      |
|    |     |     |     | 530 |     |     |     | 535 |     |     |     |     | 540 |     |     |     |      |
| 20 | CAA | AGA | GAT | GCT | TTA | CAA | CAA | GAA | GTA | GCA | TCT | CTC | CAA | GGC | AAA | CTT | 1681 |
|    | Gln | Arg | Asp | Ala | Leu | Gln | Gln | Glu | Val | Ala | Ser | Leu | Gln | Gly | Lys | Leu |      |
|    |     |     |     | 545 |     |     | 550 |     |     |     |     | 555 |     |     |     |     |      |
| 25 | TCT | CAA | GAG | AGG | AGC | TCT | AGA | TCA | CAG | GCT | TCT | GAT | ATG | CAG | ATA | GAA | 1729 |
|    | Ser | Gln | Glu | Arg | Ser | Ser | Arg | Ser | Gln | Ala | Ser | Asp | Met | Gln | Ile | Glu |      |
|    | 560 |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |      |
| 30 | CTA | GAA | GCA | AAA | TTG | CAG | GCT | CTC | CAT | ATT | GAA | CTG | GAG | CAT | GTC | AGA | 1777 |
|    | Leu | Glu | Ala | Lys | Leu | Gln | Ala | Leu | His | Ile | Glu | Leu | Glu | His | Val | Arg |      |
|    |     |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |      |
| 35 | AAT | TGT | GAA | GAC | AAA | GTT | ACC | CAA | GAC | AAC | AGA | CAA | CTA | TTG | GAA | AGG | 1825 |
|    | Asn | Cys | Glu | Asp | Lys | Val | Thr | Gln | Asp | Asn | Arg | Gln | Leu | Leu | Glu | Arg |      |
|    |     |     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |      |
| 40 | ATA | TCA | ACA | TTG | GAG | AAA | GAA | TGT | GCT | TCT | CTA | GAA | TTA | GAA | TTG | AAA | 1873 |
|    | Ile | Ser | Thr | Leu | Glu | Lys | Glu | Cys | Ala | Ser | Leu | Glu | Leu | Glu | Leu | Lys |      |
|    |     |     |     | 610 |     |     |     | 615 |     |     |     |     | 620 |     |     |     |      |
| 45 | GCA | ACA | CAA | AAC | AAA | TAT | GAG | CAA | GAG | GTC | AAA | GCA | CAT | CGC | GAA | ACT | 1921 |
|    | Ala | Thr | Gln | Asn | Lys | Tyr | Glu | Gln | Glu | Val | Lys | Ala | His | Arg | Glu | Thr |      |
|    |     |     |     | 625 |     |     | 630 |     |     |     |     | 635 |     |     |     |     |      |
| 50 | GAA | AAA | TCA | AGA | CTG | GTC | AGT | AAA | GAA | GAA | GCA | AAT | ATG | GAG | GAA | GTT | 1969 |
|    | Glu | Lys | Ser | Arg | Leu | Val | Ser | Lys | Glu | Glu | Ala | Asn | Met | Glu | Glu | Val |      |
|    |     |     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |      |
| 55 | AAA | GCA | CTC | CAA | ATA | AAA | TTA | AAT | GAA | GAG | AAA | TCT | GCT | CGA | CAG | AAA | 2017 |
|    | Lys | Ala | Leu | Gln | Ile | Lys | Leu | Asn | Glu | Glu | Lys | Ser | Ala | Arg | Gln | Lys |      |
|    |     |     |     |     | 660 |     |     |     |     | 665 |     |     |     | 670 |     |     |      |
| 60 | TCT | GAT | CAG | AAT | TCT | CAA | GAA | AAG | GAA | CGA | CAA | ATT | TCT | ATG | TTA | TCT | 2065 |
|    | Ser | Asp | Gln | Asn | Ser | Gln | Glu | Lys | Glu | Arg | Gln | Ile | Ser | Met | Leu | Ser |      |
|    |     |     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |      |
| 65 | GTG | GAT | TAT | CGT | CAA | ATC | CAA | CAG | CGT | TTG | CAA | AAG | CTA | GAA | GGA | GAA | 2113 |
|    | Val | Asp | Tyr | Arg | Gln | Ile | Gln | Gln | Arg | Leu | Gln | Lys | Leu | Glu | Gly | Glu |      |
|    |     |     |     | 690 |     |     |     | 695 |     |     |     |     | 700 |     |     |     |      |
| 70 | TAT | AGG | CAA | GAG | AGT | GAA | AAA | GTT | AAA | GCT | CTC | CAC | AGT | CAG | ATT | GAG | 2161 |
|    | Tyr | Arg | Gln | Glu | Ser | Glu | Lys | Val | Lys | Ala | Leu | His | Ser | Gln | Ile | Glu |      |
|    |     |     |     | 705 |     |     | 710 |     |     |     |     | 715 |     |     |     |     |      |
| 75 | CAA | GAG | CAA | CTA | AAA | AAA | TCA | CAA | TTA | CAA | AGC | GAA | TTG | GGT | GTT | CAA | 2209 |
|    | Gln | Glu | Gln | Leu | Lys | Lys | Ser | Gln | Leu | Gln | Ser | Glu | Leu | Gly | Val | Gln |      |
|    |     |     |     |     |     | 725 |     |     |     |     | 730 |     |     |     |     | 735 |      |
| 80 | AGG | TCT | CAG | ACT | GCA | CAT | TTA | ACA | GCC | AGG | GAA | GCT | CAG | CTA | GTT | GGA | 2257 |
|    | Arg | Ser | Gln | Thr | Ala | His | Leu | Thr | Ala | Arg | Glu | Ala | Gln | Leu | Val | Gly |      |
|    |     |     |     |     | 740 |     |     |     |     | 745 |     |     |     |     | 750 |     |      |
| 85 | GAA | GTT | GCT | CAT | CTT | AGA | GAT | GCT | AAA | AGA | AAT | GTT | GAA | GAA | GAG | TTA | 2305 |

Glu Val Ala His Leu Arg Asp Ala Lys Arg Asn Val Glu Glu Glu Leu  
 755 760 765  
 5 CAC AAG TTA AAA ACT GCT CGA TCA GTG GAT AAT GCT CAG ATG AAA GAG 2353  
 His Lys Leu Lys Thr Ala Arg Ser Val Asp Asn Ala Gln Met Lys Glu  
 770 775 780  
 10 CTT CAA GAA CAA GTT GAA GCC GAG CAA GTT TTC TCG ACT CTT TAT AAA 2401  
 Leu Gln Glu Gln Val Glu Ala Glu Gln Val Phe Ser Thr Leu Tyr Lys  
 785 790 795  
 15 ACA CAT TCT AAT GAA CTT AAG GAA GAA CTT GAG GAA AAA TCT CGT CAT 2449  
 Thr His Ser Asn Glu Leu Lys Glu Glu Leu Glu Glu Lys Ser Arg His  
 800 805 810 815  
 ATT CAA GAA ATG GAA GAA GAA AGA GAA AGT TTG GTT CAT CAG CTA CAA 2497  
 Ile Gln Glu Met Glu Glu Glu Arg Glu Ser Leu Val His Gln Leu Gln  
 820 825 830  
 20 ATT GCA TTA GCT AGA GCT GAT TCA GAG GCA TTG GCG AGA TCA ATA GCT 2545  
 Ile Ala Leu Ala Arg Ala Asp Ser Glu Ala Leu Ala Arg Ser Ile Ala  
 835 840 845  
 25 GAT GAA AGT ATA GCT GAT TTA GAA AAG GAA AAG ACT ATG AAG GAA TTA 2593  
 Asp Glu Ser Ile Ala Asp Leu Glu Lys Glu Lys Thr Met Lys Glu Leu  
 850 855 860  
 30 GAA CTA AAA GAA TTA TTA AAC AAA AAT CGT ACT GAA CTT TCC CAG AAA 2641  
 Glu Leu Lys Glu Leu Leu Asn Lys Asn Arg Thr Glu Leu Ser Gln Lys  
 865 870 875  
 35 GAC ATT TCA ATA AGT GCA TTG CGT GAA CGA GAA AAT GAA CAG AAG AAA 2689  
 Asp Ile Ser Ile Ser Ala Leu Arg Glu Arg Glu Asn Glu Gln Lys Lys  
 880 885 890 895  
 CTT TTA GAA CAA ATC TC 2706  
 Leu Leu Glu Gln Ile  
 900

## (2) INFORMATION FOR SEQ ID NO:21:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 900 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Met Lys Ser Ile Glu Ala Tyr Thr Asn Arg Tyr Glu Ile Ile Ala Ser  
 1 5 10 15  
 55 Glu Ile Val Asn Leu Arg Met Lys Pro Asp Asp Phe Asn Leu Ile Lys  
 20 25 30  
 Val Ile Gly Arg Gly Ala Phe Gly Glu Val Gln Leu Val Arg His Lys  
 35 40 45  
 60 Ser Thr Ala Gln Val Phe Ala Met Lys Arg Leu Ser Lys Phe Glu Met  
 50 55 60  
 65 Ile Lys Arg Pro Asp Ser Ala Phe Phe Trp Glu Glu Arg His Ile Met  
 65 70 75 80  
 Ala His Ala Lys Ser Glu Trp Ile Val Gln Leu His Phe Ala Phe Gln  
 85 90 95

Asp Gln Lys Tyr Leu Tyr Met Val Met Asp Tyr Met Pro Gly Gly Asp  
 100 105 110  
 5 Leu Val Ser Leu Met Ser Asp Tyr Glu Ile Pro Glu Lys Trp Ala Met  
 115 120 125  
 Phe Tyr Thr Met Glu Val Val Leu Ala Leu Asp Thr Ile His Ser Met  
 130 135 140  
 10 Gly Phe Val His Arg Asp Val Lys Pro Asp Asn Met Leu Leu Asp Lys  
 145 150 155 160  
 Tyr Gly His Leu Lys Leu Ala Asp Phe Gly Thr Cys Met Lys Met Asp  
 165 170 175  
 15 Thr Asp Gly Leu Val Arg Ser Asn Asn Ala Val Gly Thr Pro Asp Tyr  
 180 185 190  
 20 Ile Ser Pro Glu Val Leu Gln Ser Gln Gly Gly Glu Gly Val Tyr Gly  
 195 200 205  
 Arg Glu Cys Asp Trp Trp Ser Val Gly Ile Phe Leu Tyr Glu Met Leu  
 210 215 220  
 25 Phe Gly Glu Thr Pro Phe Tyr Ala Asp Ser Leu Val Gly Thr Tyr Ser  
 225 230 235 240  
 Lys Ile Met Asp His Arg Asn Ser Leu Thr Phe Pro Pro Glu Val Glu  
 245 250 255  
 30 Ile Ser Gln Tyr Ala Arg Ser Leu Ile Gln Gly Phe Leu Thr Asp Arg  
 260 265 270  
 35 Thr Gln Arg Leu Gly Arg Asn Glu Val Glu Glu Ile Lys Arg His Pro  
 275 280 285  
 Phe Phe Ile Asn Asp Gln Trp Thr Phe Asp Asn Leu Arg Asp Ser Ala  
 290 295 300  
 40 Pro Pro Val Val Pro Glu Leu Ser Gly Asp Asp Asp Thr Arg Asn Phe  
 305 310 315 320  
 Asp Asp Ile Glu Arg Asp Glu Thr Pro Glu Glu Asn Phe Pro Ile Pro  
 325 330 335  
 45 Lys Thr Phe Ala Gly Asn His Leu Pro Phe Val Gly Phe Thr Tyr Asn  
 340 345 350  
 50 Gly Asp Tyr Gln Leu Leu Thr Asn Gly Gly Val Arg Asn Ser Asp Met  
 355 360 365  
 Val Asp Thr Lys Leu Asn Asn Ile Cys Val Ser Ser Lys Asp Asp Val  
 370 375 380  
 55 Leu Asn Leu Gln Asn Leu Leu Glu Gln Glu Lys Gly Asn Ser Glu Asn  
 385 390 395 400  
 60 Leu Lys Thr Asn Thr Gln Leu Leu Ser Asn Lys Leu Asp Glu Leu Gly  
 405 410 415  
 Gln Arg Glu Cys Glu Leu Arg Asn Gln Ala Gly Asp Tyr Glu Lys Glu  
 420 425 430  
 65 Leu Thr Lys Phe Lys Leu Ser Cys Lys Glu Leu Gln Arg Lys Ala Glu  
 435 440 445  
 Phe Glu Asn Glu Leu Arg Arg Lys Thr Glu Ser Leu Leu Val Glu Thr  
 450 455 460

Lys Lys Arg Leu Asp Glu Glu Gln Asn Lys Arg Thr Arg Glu Met Asn  
 465 470 475 480  
 5 Asn Asn Gln Gln His Asn Asp Lys Ile Asn Met Leu Glu Lys Gln Ile  
 485 490 495  
 Asn Asp Leu Gln Glu Lys Leu Lys Gly Glu Leu Glu His Asn Gln Lys  
 500 505 510  
 10 Leu Lys Lys Gln Ala Val Glu Leu Arg Val Ala Gln Ser Ala Thr Glu  
 515 520 525  
 Gln Leu Asn Asn Glu Leu Gln Glu Thr Met Gln Gly Leu Gln Thr Gln  
 530 535 540  
 15 Arg Asp Ala Leu Gln Gln Glu Val Ala Ser Leu Gln Gly Lys Leu Ser  
 545 550 555 560  
 20 Gln Glu Arg Ser Ser Arg Ser Gln Ala Ser Asp Met Gln Ile Glu Leu  
 565 570 575  
 Glu Ala Lys Leu Gln Ala Leu His Ile Glu Leu Glu His Val Arg Asn  
 580 585 590  
 25 Cys Glu Asp Lys Val Thr Gln Asp Asn Arg Gln Leu Leu Glu Arg Ile  
 595 600 605  
 Ser Thr Leu Glu Lys Glu Cys Ala Ser Leu Glu Leu Glu Leu Lys Ala  
 610 615 620  
 30 Thr Gln Asn Lys Tyr Glu Gln Glu Val Lys Ala His Arg Glu Thr Glu  
 625 630 635 640  
 35 Lys Ser Arg Leu Val Ser Lys Glu Glu Ala Asn Met Glu Glu Val Lys  
 645 650 655  
 Ala Leu Gln Ile Lys Leu Asn Glu Glu Lys Ser Ala Arg Gln Lys Ser  
 660 665 670  
 40 Asp Gln Asn Ser Gln Glu Lys Glu Arg Gln Ile Ser Met Leu Ser Val  
 675 680 685  
 Asp Tyr Arg Gln Ile Gln Gln Arg Leu Gln Lys Leu Glu Gly Glu Tyr  
 690 695 700  
 45 Arg Gln Glu Ser Glu Lys Val Lys Ala Leu His Ser Gln Ile Glu Gln  
 705 710 715 720  
 50 Glu Gln Leu Lys Lys Ser Gln Leu Gln Ser Glu Leu Gly Val Gln Arg  
 725 730 735  
 Ser Gln Thr Ala His Leu Thr Ala Arg Glu Ala Gln Leu Val Gly Glu  
 740 745 750  
 55 Val Ala His Leu Arg Asp Ala Lys Arg Asn Val Glu Glu Glu Leu His  
 755 760 765  
 Lys Leu Lys Thr Ala Arg Ser Val Asp Asn Ala Gln Met Lys Glu Leu  
 770 775 780  
 60 Gln Glu Gln Val Glu Ala Glu Gln Val Phe Ser Thr Leu Tyr Lys Thr  
 785 790 795 800  
 65 His Ser Asn Glu Leu Lys Glu Glu Leu Glu Glu Lys Ser Arg His Ile  
 805 810 815  
 Gln Glu Met Glu Glu Glu Arg Glu Ser Leu Val His Gln Leu Gln Ile  
 820 825 830

Ala Leu Ala Arg Ala Asp Ser Glu Ala Leu Ala Arg Ser Ile Ala Asp  
835 840 845

5 Glu Ser Ile Ala Asp Leu Glu Lys Glu Lys Thr Met Lys Glu Leu Glu  
850 855 860

Leu Lys Glu Leu Leu Asn Lys Asn Arg Thr Glu Leu Ser Gln Lys Asp  
865 870 875 880

10 Ile Ser Ile Ser Ala Leu Arg Glu Arg Glu Asn Glu Gln Lys Lys Leu  
885 890 895

Leu Glu Gln Ile  
900

15

(2) INFORMATION FOR SEQ ID NO:22:

20 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 414 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: cDNA

(ix) FEATURE:  
(A) NAME/KEY: CDS  
(B) LOCATION: 3..414

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

35 GA GCT GAT GAG AAT GGA AAT GTG ATT AGC ATT ACT GAT GAA AAT GGA 47  
Ala Asp Glu Asn Gly Asn Val Ile Ser Ile Thr Asp Glu Asn Gly  
1 5 10 15

AAC ATT ATT AGT ACT ACT GAT GAG AAT GGA AAT GTG ATT AGC ATT ACT 95  
Asn Ile Ile Ser Thr Thr Asp Glu Asn Gly Asn Val Ile Ser Ile Thr  
20 25 30

GAT GAG AAT GGA AAC ATT ATT AGT ACT ACT GAT GAG AAT GGA AAT GTG 143  
Asp Glu Asn Gly Asn Ile Ile Ser Thr Thr Asp Glu Asn Gly Asn Val  
35 40 45

45 ATT AGC ATT ACT GAT GAA AAT GGA AAC ATT ATT AGT ACT ACT GAT GAG  
Ile Ser Ile Thr Asp Glu Asn Gly Asn Ile Ile Ser Thr Thr Asp Glu  
50 55 60

50 AAT GGA AAT GTG ATT AGC ATT ACT GAT GAG AAT GGA AAT GTG ATT AGC 239  
Asn Gly Asn Val Ile Ser Ile Thr Asp Glu Asn Gly Asn Val Ile Ser  
65 70 75

55 ATT ACT GAT GAA AAT GGA AAC TCG AAT AGC ACT ACT AGT GTT TTC AAT 287  
Ile Thr Asp Glu Asn Gly Asn Ser Asn Ser Thr Thr Ser Val Phe Asn  
80 85 90 95

60 GAA ACT GAA AAT ATG ACT GGT GCT GCT GAT ACA AAT GAA TAT TCA ATT 335  
Glu Thr Glu Asn Met Thr Gly Ala Ala Asp Thr Asn Glu Tyr Ser Ile  
100 105 110

65 GGT TCT ACT GAC GGA AAT GGA AAT TTT ATA AGT ACT TTT AGT GAT CAT 383  
Gly Ser Thr Asp Gly Asn Gly Asn Phe Ile Ser Thr Phe Ser Asp His  
115 120 125

GAT TAC GTA AGT AAT ACT GAA GAA AAT GAA A 414  
Asp Tyr Val Ser Asn Thr Glu Glu Asn Glu  
130 135

## (2) INFORMATION FOR SEQ ID NO:23:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 137 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Ala Asp Glu Asn Gly Asn Val Ile Ser Ile Thr Asp Glu Asn Gly Asn  
 1 5 10 15  
 Ile Ile Ser Thr Thr Asp Glu Asn Gly Asn Val Ile Ser Ile Thr Asp  
 20 25 30  
 Glu Asn Gly Asn Ile Ile Ser Thr Thr Asp Glu Asn Gly Asn Val Ile  
 35 40 45  
 Ser Ile Thr Asp Glu Asn Gly Asn Ile Ile Ser Thr Thr Asp Glu Asn  
 50 55 60  
 Gly Asn Val Ile Ser Ile Thr Asp Glu Asn Gly Asn Val Ile Ser Ile  
 65 70 75 80  
 Thr Asp Glu Asn Gly Asn Ser Asn Ser Thr Thr Ser Val Phe Asn Glu  
 85 90 95  
 Thr Glu Asn Met Thr Gly Ala Ala Asp Thr Asn Glu Tyr Ser Ile Gly  
 100 105 110  
 Ser Thr Asp Gly Asn Gly Asn Phe Ile Ser Thr Phe Ser Asp His Asp  
 115 120 125  
 Tyr Val Ser Asn Thr Glu Glu Asn Glu  
 130 135

## (2) INFORMATION FOR SEQ ID NO:24:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 273 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 3..273

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

AT GAG AAT GGA AAT GTG ATT AGC TAT ACT GAT GAA AAT GGA AAC ATT 47  
 Glu Asn Gly Asn Val Ile Ser Tyr Thr Asp Glu Asn Gly Asn Ile  
 1 5 10 15  
 ATC AGT ACT ACT GAT GAG AAT GGA AAT GTG ATT AGC ATT ACT GAT GAA 95  
 Ile Ser Thr Thr Asp Glu Asn Gly Asn Val Ile Ser Ile Thr Asp Glu  
 20 25 30  
 AAT GGA AAT GTG ATT AGC ATT ACT GAT GAA AAT GGA AAC ATT ATC AGT 143  
 Asn Gly Asn Val Ile Ser Ile Thr Asp Glu Asn Gly Asn Ile Ile Ser  
 35 40 45



ACT ACT GAT GAG AAT GGA AAT GTG ATT AGC ATT ACT GAT GAA AAT GGA 191  
 Thr Thr Asp Glu Asn Gly Asn Val Ile Ser Ile Thr Asp Glu Asn Gly  
           50                          55                          60

5 AAT GTG ATT AGC ATT ACT GAT GAA AAT GGA AAC ATT ATT AGT ACT ACT 239  
 Asn Val Ile Ser Ile Thr Asp Glu Asn Gly Asn Ile Ile Ser Thr Thr  
           65                          70                          75

10 GAT GAG AAT GGA AAT GTG ATT AGC AAT ACT CGA G 273  
 Asp Glu Asn Gly Asn Val Ile Ser Asn Thr Arg  
           80                          85                          90

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 90 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Glu Asn Gly Asn Val Ile Ser Tyr Thr Asp Glu Asn Gly Asn Ile Ile  
   1                          5                          10                          15  
 Ser Thr Thr Asp Glu Asn Gly Asn Val Ile Ser Ile Thr Asp Glu Asn  
           20                          25                          30  
 Gly Asn Val Ile Ser Ile Thr Asp Glu Asn Gly Asn Ile Ile Ser Thr  
           35                          40                          45  
 Thr Asp Glu Asn Gly Asn Val Ile Ser Ile Thr Asp Glu Asn Gly Asn  
           50                          55                          60  
 Val Ile Ser Ile Thr Asp Glu Asn Gly Asn Ile Ile Ser Thr Thr Asp  
           65                          70                          75                          80  
 Glu Asn Gly Asn Val Ile Ser Asn Thr Arg  
                           85                          90

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1704 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 24..1406

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CAGAAACCCG ACATTCTCAA AAT ATG GAA CCT CAA TCG CTG TCT TGG CAA 50  
                           Met Glu Pro Gln Ser Leu Ser Trp Gln  
                           1                          5  
 CTT CCG ACT CAA GTA GTT CAG CCA GTT TTT GAA CAA CAA ATG CAG ATT 98  
 Leu Pro Thr Gln Val Val Gln Pro Val Phe Glu Gln Gln Met Gln Ile  
   10                          15                          20                          25  
 CCT GGA TAT AAT ATG CAA ATT CAA TCT AAT TAT TAT CAA ATT CAC CCA 146

|    | Pro | Gly | Tyr | Asn | Met | Gln | Ile | Gln | Ser | Asn | Tyr | Tyr | Gln | Ile | His | Pro |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    |     |     |     |     | 30  |     |     |     |     | 35  |     |     |     |     |     | 40  |     |
| 5  | GAA | ATG | TTG | GAT | CCA | AAT | TTG | AAC | AAT | CCT | CAG | CAG | TTA | ATG | TTT | AAT | 194 |
|    | Glu | Met | Leu | Asp | Pro | Asn | Leu | Asn | Asn | Pro | Gln | Gln | Leu | Met | Phe | Asn |     |
|    |     |     |     | 45  |     |     |     |     | 50  |     |     |     |     | 55  |     |     |     |
| 10 | TAT | ATG | CAA | TTA | CAA | CAA | TTG | CAG | GAA | CTA | CAA | CAT | TTA | AGT | CAA | CAA | 242 |
|    | Tyr | Met | Gln | Leu | Gln | Gln | Leu | Gln | Glu | Leu | Gln | His | Leu | Ser | Gln | Gln |     |
|    |     |     | 60  |     |     |     |     | 65  |     |     |     |     | 70  |     |     |     |     |
| 15 | CAG | CCA | ATG | CAT | CAT | GAA | TTT | GAA | CAT | CAT | ATC | CCC | ATT | CCA | CAA | GAA | 290 |
|    | Gln | Pro | Met | His | His | Glu | Phe | Glu | His | His | Ile | Pro | Ile | Pro | Gln | Glu |     |
|    |     |     | 75  |     |     |     | 80  |     |     |     |     | 85  |     |     |     |     |     |
| 20 | GCA | ACT | TCA | ACT | AAT | TAC | GGT | CCA | TCC | GGA | CAG | TAT | ATT | ACT | AGT | GAC | 338 |
|    | Ala | Thr | Ser | Thr | Asn | Tyr | Gly | Pro | Ser | Gly | Gln | Tyr | Ile | Thr | Ser | Asp |     |
|    |     |     |     |     |     | -95 |     |     |     |     | 100 |     |     |     |     | 105 |     |
|    |     |     | 90  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 25 | GCA | ACA | TCT | TAT | CAA | TCA | ATT | GCC | CAA | CAA | TTT | GTA | CCA | CAA | CCA | CCA | 386 |
|    | Ala | Thr | Ser | Tyr | Gln | Ser | Ile | Ala | Gln | Gln | Phe | Val | Pro | Gln | Pro | Pro |     |
|    |     |     |     |     |     |     |     |     |     |     | 115 |     |     |     |     | 120 |     |
|    |     |     |     |     | 110 |     |     |     |     |     |     |     |     |     |     |     |     |
| 30 | ATT | GAA | ACT | ACC | ACC | ACG | AAA | ATA | CCT | GAA | ACT | GAA | ATT | CAA | ATT | GGC | 434 |
|    | Ile | Glu | Thr | Thr | Thr | Thr | Lys | Ile | Pro | Glu | Thr | Glu | Ile | Gln | Ile | Gly |     |
|    |     |     |     |     |     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |
|    |     |     |     | 125 |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 35 | GTT | TCG | AAT | CAA | TAT | GCC | CAA | AAT | ATA | ACT | TAT | AAT | TCA | AAT | ATC | AGT | 482 |
|    | Val | Ser | Asn | Gln | Tyr | Ala | Gln | Asn | Ile | Thr | Tyr | Asn | Ser | Asn | Ile | Ser |     |
|    |     |     |     |     |     |     |     | 145 |     |     |     |     | 150 |     |     |     |     |
|    |     |     | 140 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 40 | CCT | GAA | GTG | ATT | GGA | TTC | CGA | GAA | CAT | TAT | GTT | GCG | GAA | CAG | CCT | TCT | 530 |
|    | Pro | Glu | Val | Ile | Gly | Phe | Arg | Glu | His | Tyr | Val | Ala | Glu | Gln | Pro | Ser |     |
|    |     |     |     |     |     |     | 160 |     |     |     |     | 165 |     |     |     |     |     |
|    |     |     | 155 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 45 | GGT | GAC | GTG | CTT | CAC | AAA | AGT | CAT | TTA | ACA | GAA | CAA | CCA | GCA | GAT | AAA | 578 |
|    | Gly | Asp | Val | Leu | His | Lys | Ser | His | Leu | Thr | Glu | Gln | Pro | Ala | Asp | Lys |     |
|    |     |     |     |     |     | 175 |     |     |     |     | 180 |     |     |     |     | 185 |     |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    |     |     | 170 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 50 | AGC | ACA | CGT | GGT | GAT | CAG | GAA | CCT | GTT | AGT | GAG | ACA | GGC | TCT | GGT | TTT | 626 |
|    | Ser | Thr | Arg | Gly | Asp | Gln | Glu | Pro | Val | Ser | Glu | Thr | Gly | Ser | Gly | Phe |     |
|    |     |     |     |     |     |     |     |     |     | 195 |     |     |     |     | 200 |     |     |
|    |     |     |     |     |     | 190 |     |     |     |     |     |     |     |     |     |     |     |
| 55 | TCG | TAT | GCA | CAA | ATT | TTA | TCA | CAG | GGA | CTT | AAG | CCT | ACC | CAG | CCA | TCC | 674 |
|    | Ser | Tyr | Ala | Gln | Ile | Leu | Ser | Gln | Gly | Leu | Lys | Pro | Thr | Gln | Pro | Ser |     |
|    |     |     |     |     |     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |
|    |     |     |     | 205 |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 60 | AAC | TCA | GTT | AAT | TTG | CTT | GCA | GAT | CGA | TCG | AGA | TCA | CCT | CTA | GAT | ACG | 722 |
|    | Asn | Ser | Val | Asn | Leu | Leu | Ala | Asp | Arg | Ser | Arg | Ser | Pro | Leu | Asp | Thr |     |
|    |     |     |     |     |     |     |     | 225 |     |     |     |     | 230 |     |     |     |     |
|    |     |     | 220 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 65 | AAA | ACG | AAA | GAA | AAT | TAT | AAA | TCT | CCT | GGT | CGT | GTG | CAG | GAT | ATC | ACG | 770 |
|    | Lys | Thr | Lys | Glu | Asn | Tyr | Lys | Ser | Pro | Gly | Arg | Val | Gln | Asp | Ile | Thr |     |
|    |     |     |     |     |     |     | 240 |     |     |     |     | 245 |     |     |     |     |     |
|    |     |     | 235 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 70 | AAA | ATA | ATA | GAT | GAG | AAA | CAA | AAG | TCG | TCA | AAA | GAC | ACA | GAG | TGG | CAT | 818 |
|    | Lys | Ile | Ile | Asp | Glu | Lys | Gln | Lys | Ser | Ser | Lys | Asp | Thr | Glu | Trp | His |     |
|    |     |     |     |     |     |     | 255 |     |     |     | 260 |     |     |     | 265 |     |     |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    |     |     | 250 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 75 | AAT | AAG | AAA | GTG | AAA | GAA | CAT | AAA | AAA | GTG | AAA | GAT | ATC | AAA | CCT | GAT | 866 |
|    | Asn | Lys | Lys | Val | Lys | Glu | His | Lys | Lys | Val | Lys | Asp | Ile | Lys | Pro | Asp |     |
|    |     |     |     |     |     |     |     |     |     | 275 |     |     |     | 280 |     |     |     |
|    |     |     |     |     |     | 270 |     |     |     |     |     |     |     |     |     |     |     |
| 80 | TTC | GAA | TCT | TCT | CAA | AGG | AAT | AAG | AAA | AGC | AAG | AAT | ATT | CCT | AAG | CAA | 914 |
|    | Phe | Glu | Ser | Ser | Gln | Arg | Asn | Lys | Lys | Ser | Lys | Asn | Ile | Pro | Lys | Gln |     |
|    |     |     |     |     |     |     |     |     | 290 |     |     |     |     | 295 |     |     |     |
|    |     |     |     | 285 |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 85 | ATT | GAA | AAT | ATC | ACA | CCT | CAA | CTT | GAC | AGC | TTA | CGA | TCA | CGA | GAT | ATA | 962 |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

|    | Ile        | Glu        | Asn        | Ile        | Thr        | Pro        | Gln        | Leu        | Asp        | Ser | Leu | Arg | Ser | Arg | Asp | Ile |      |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|-----|-----|-----|-----|-----|-----|-----|------|
|    | 300        |            |            |            |            |            | 305        |            |            | 310 |     |     |     |     |     |     |      |
| 5  | GTA        | ATT        | AAG        | GGA        | GAA        | TTA        | CTA        | ACA        | AAA        | GAT | ACT | ACA | AAA | AGT | TTA | ACT | 1010 |
|    | Val        | Ile        | Lys        | Gly        | Glu        | Leu        | Thr        | Lys        | Asp        | Thr | Thr | Lys | Ser | Leu | Thr |     |      |
|    | 315        |            |            | 320        |            |            |            | 325        |            |     |     |     |     |     |     |     |      |
| 10 | ACT        | GTT        | AAT        | GTT        | GAT        | AGT        | GAA        | TTA        | GAT        | AGT | GTA | AAA | CCT | AAA | GAT | GAA | 1058 |
|    | Thr        | Val        | Asn        | Val        | Asp        | Ser        | Glu        | Leu        | Asp        | Ser | Val | Lys | Pro | Lys | Asp | Glu |      |
|    | 330        |            |            | 335        |            |            |            | 340        |            |     |     |     |     |     | 345 |     |      |
| 15 | AAA        | CCT        | GAA        | CCT        | TCT        | GAA        | CCT        | AGT        | AAA        | ACG | TTT | ATT | GAT | ACT | TCA | GTT | 1106 |
|    | Lys        | Pro        | Glu        | Pro        | Ser        | Glu        | Pro        | Ser        | Lys        | Thr | Phe | Ile | Asp | Thr | Ser | Val |      |
|    |            |            |            | 350        |            |            |            | 355        |            |     |     |     |     |     | 360 |     |      |
| 20 | GCA        | AAG        | GAT        | GTT        | GAT        | AAT        | TCT        | ACA        | CAG        | GCG | AAC | CAT | AAA | AAG | AAG | AAA | 1154 |
|    | Ala        | Lys        | Asp        | Val        | Asp        | Asn        | Ser        | Thr        | Gln        | Ala | Asn | His | Lys | Lys | Lys | Lys |      |
|    | 365        |            |            |            |            |            |            | 370        |            |     |     | 375 |     |     |     |     |      |
| 25 | AGT        | AAA        | TCT        | AAG        | CCG        | AGG        | AAA        | ACG        | GAA        | CCG | GAA | GAT | GAA | ATT | GAA | AAA | 1202 |
|    | Ser        | Lys        | Ser        | Lys        | Pro        | Arg        | Lys        | Thr        | Glu        | Pro | Glu | Asp | Glu | Ile | Glu | Lys |      |
|    | 380        |            |            |            |            |            |            | 385        |            |     |     | 390 |     |     |     |     |      |
| 30 | GCT        | TTG        | AAA        | GAA        | ATT        | CAA        | GCT        | AGT        | GAG        | AAA | AAA | CTT | ACG | AAG | TCT | ATC | 1250 |
|    | Ala        | Leu        | Lys        | Glu        | Ile        | Gln        | Ala        | Ser        | Glu        | Lys | Lys | Leu | Thr | Lys | Ser | Ile |      |
|    | 395        |            |            | 400        |            |            |            | 405        |            |     |     |     |     |     |     |     |      |
| 35 | GAT        | AAC        | ATT        | GTG        | AAT        | AAA        | TTT        | AAT        | ACA        | CCA | CTT | GCT | AGT | GTT | AAA | GCC | 1298 |
|    | Asp        | Asn        | Ile        | Val        | Asn        | Lys        | Phe        | Asn        | Thr        | Pro | Leu | Ala | Ser | Val | Lys | Ala |      |
|    | 410        |            |            | 415        |            |            |            | 420        |            |     |     |     |     |     | 425 |     |      |
| 40 | GAT        | GAT        | TCC        | AAT        | TCT        | ACC        | AAG        | GAT        | AAT        | GTA | CCA | GCA | AAG | AAG | AAA | AAA | 1346 |
|    | Asp        | Asp        | Ser        | Asn        | Ser        | Thr        | Lys        | Asp        | Asn        | Val | Pro | Ala | Lys | Lys | Lys | Lys |      |
|    |            |            |            | 430        |            |            |            | 435        |            |     |     | 440 |     |     |     |     |      |
| 45 | CCT        | TCG        | AAG        | TCA        | TCT        | GTT        | TCT        | TTA        | CCT        | GAG | AAT | GTA | GTA | CAA | AAT | CTA | 1394 |
|    | Pro        | Ser        | Lys        | Ser        | Ser        | Val        | Ser        | Leu        | Pro        | Glu | Asn | Val | Val | Gln | Asn | Leu |      |
|    | 445        |            |            |            |            |            |            | 450        |            |     |     | 455 |     |     |     |     |      |
| 50 | TTG        | ATA        | CTA        | ACA        | TAA        | CTACTAGTAG | CGACAAGATT | GAAAACATGC | CGCAACCGCA |     |     |     |     |     |     |     | 1449 |
|    | Leu        | Ile        | Leu        | Thr        |            |            |            |            |            |     |     |     |     |     |     |     |      |
|    | 460        |            |            |            |            |            |            |            |            |     |     |     |     |     |     |     |      |
| 55 | ACCAAAAAGA | GAAGATTAC  | AAGATGCAGC | TAAGGAAGTA | TTGACTTCAA | TAGAGTCAGT |            |            |            |     |     |     |     |     |     |     | 1509 |
| 60 | AATGATGCAG | TCTGTTGAGA | CTATTCCTAT | TACGAAGAAA | AGAGTAAATA | AGAAAAAGAA |            |            |            |     |     |     |     |     |     |     | 1569 |
|    | TACCACTCAA | CAGACGAAGG | AATTTGTGGA | ACACGAAATA | TGCGATACAT | CAAAAAATGA |            |            |            |     |     |     |     |     |     |     | 1629 |
| 65 | AACTTTAAAA | AATATTGAAA | AAGAATCGCA | TGAGAATATG | GCTATATTGC | AAACAAGTCC |            |            |            |     |     |     |     |     |     |     | 1689 |
|    | GAAACCGCCA | CTAAG      |            |            |            |            |            |            |            |     |     |     |     |     |     |     | 1704 |

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 461 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Glu | Pro | Gln | Ser | Leu | Ser | Trp | Gln | Leu | Pro | Thr | Gln | Val | Val | Gln |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |     |

Pro Val Phe Glu Gln Gln Met Gln Ile Pro Gly Tyr Asn Met Gln Ile  
 20 25 30  
 5 Gln Ser Asn Tyr Tyr Gln Ile His Pro Glu Met Leu Asp Pro Asn Leu  
 35 40 45  
 Asn Asn Pro Gln Gln Leu Met Phe Asn Tyr Met Gln Leu Gln Gln Leu  
 50 55 60  
 10 Gln Glu Leu Gln His Leu Ser Gln Gln Gln Pro Met His His Glu Phe  
 65 70 75 80  
 Glu His His Ile Pro Ile Pro Gln Glu Ala Thr Ser Thr Asn Tyr Gly  
 85 90 95  
 15 Pro Ser Gly Gln Tyr Ile Thr Ser Asp Ala Thr Ser Tyr Gln Ser Ile  
 100 105 110  
 20 Ala Gln Gln Phe Val Pro Gln Pro Pro Ile Glu Thr Thr Thr Thr Lys  
 115 120 125  
 Ile Pro Glu Thr Glu Ile Gln Ile Gly Val Ser Asn Gln Tyr Ala Gln  
 130 135 140  
 25 Asn Ile Thr Tyr Asn Ser Asn Ile Ser Pro Glu Val Ile Gly Phe Arg  
 145 150 155 160  
 Glu His Tyr Val Ala Glu Gln Pro Ser Gly Asp Val Leu His Lys Ser  
 165 170 175  
 30 His Leu Thr Glu Gln Pro Ala Asp Lys Ser Thr Arg Gly Asp Gln Glu  
 180 185 190  
 35 Pro Val Ser Glu Thr Gly Ser Gly Phe Ser Tyr Ala Gln Ile Leu Ser  
 195 200 205  
 Gln Gly Leu Lys Pro Thr Gln Pro Ser Asn Ser Val Asn Leu Leu Ala  
 210 215 220  
 40 Asp Arg Ser Arg Ser Pro Leu Asp Thr Lys Thr Lys Glu Asn Tyr Lys  
 225 230 235 240  
 Ser Pro Gly Arg Val Gln Asp Ile Thr Lys Ile Ile Asp Glu Lys Gln  
 245 250 255  
 45 Lys Ser Ser Lys Asp Thr Glu Trp His Asn Lys Lys Val Lys Glu His  
 260 265 270  
 50 Lys Lys Val Lys Asp Ile Lys Pro Asp Phe Glu Ser Ser Gln Arg Asn  
 275 280 285  
 Lys Lys Ser Lys Asn Ile Pro Lys Gln Ile Glu Asn Ile Thr Pro Gln  
 290 295 300  
 55 Leu Asp Ser Leu Arg Ser Arg Asp Ile Val Ile Lys Gly Glu Leu Leu  
 305 310 315 320  
 60 Thr Lys Asp Thr Thr Lys Ser Leu Thr Thr Val Asn Val Asp Ser Glu  
 325 330 335  
 Leu Asp Ser Val Lys Pro Lys Asp Glu Lys Pro Glu Pro Ser Glu Pro  
 340 345 350  
 65 Ser Lys Thr Phe Ile Asp Thr Ser Val Ala Lys Asp Val Asp Asn Ser  
 355 360 365  
 Thr Gln Ala Asn His Lys Lys Lys Lys Ser Lys Ser Lys Pro Arg Lys  
 370 375 380

Thr Glu Pro Glu Asp Glu Ile Glu Lys Ala Leu Lys Glu Ile Gln Ala  
385 390 395 400

Ser Glu Lys Lys Leu Thr Lys Ser Ile Asp Asn Ile Val Asn Lys Phe  
405 410 415

Asn Thr Pro Leu Ala Ser Val Lys Ala Asp Asp Ser Asn Ser Thr Lys  
420 425 430

Asp Asn Val Pro Ala Lys Lys Lys Lys Pro Ser Lys Ser Ser Val Ser  
435 440 445

Leu Pro Glu Asn Val Val Gln Asn Leu Leu Ile Leu Thr  
450 455 460

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1383 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

|   |      |
|---|------|
| ATGGAACCTC AATCGCTGTC TTGGCAACTT CCGACTCAAG TAGTTCAGCC AGTTTTTGAA | 60   |
| CAACAAATGC AGATTCCTGG ATATAATATG CAAATTCAT CTAATTATTA TCAAATTCAC  | 120  |
| CCAGAAATGT TGGATCCAAA TTTGAACAAT CCTCAGCAGT TAATGTTTAA TTATATGCAA | 180  |
| TTACAACAAT TGCAGGAACT ACAACATTTA AGTCAACAAC AGCCAATGCA TCATGAATTT | 240  |
| GAACATCATA TCCCCATTC ACAAGAAGCA ACTTCAACTA ATTACGGTCC ATCCGGACAG  | 300  |
| TATATTACTA GTGACGCAAC ATCTTATCAA TCAATTGCCC AACAATTGTG ACCACAACCA | 360  |
| CCAATTGAAA CTACCACCAC GAAAATACCT GAAACTGAAA TTCAAATTGG CGTTTCGAAT | 420  |
| CAATATGCCC AAAATATAAC TTATAATCA AATATCAGTC CTGAAGTGAT TGGATTCCGA  | 480  |
| GAACATTATG TTGCGGAACA GCCTTCTGGT GACGTGCTTC ACAAAGTCA TTTAACAGAA  | 540  |
| CAACCAGCAG ATAAAAGCAC ACGTGGTGAT CAGGAACCTG TTAGTGAGAC AGGCTCTGGT | 600  |
| TTTTCGTATG CACAAATTTT ATCACAGGGA CTTAAGCCTA CCCAGCCATC CAACTCAGTT | 660  |
| AATTTGCTTG CAGATCGATC GAGATCACCT CTAGATACGA AAACGAAAGA AAATTATAAA | 720  |
| TCTCCTGGTC GTGTGCAGGA TATCACGAAA ATAATAGATG AGAAACAAA GTCGTCAAAA  | 780  |
| GACACAGAGT GGCATAATAA GAAAGTGAAA GAACATAAAA AAGTGAAAGA TATCAAACCT | 840  |
| GATTTGGAAT CTTCTCAAAG GAATAAGAAA AGCAAGAATA TTCCTAAGCA AATTGAAAAT | 900  |
| ATCACACCTC AACTTGACAG CTTACGATCA CGAGATATAG TAATTAAGGG AGAATTACTA | 960  |
| ACAAAAGATA CTACAAAAG TTTAACTACT GTTAATGTTG ATAGTGAATT AGATAGTGTA  | 1020 |
| AAACCTAAAG ATGAAAAACC TGAACCTTCT GAACCTAGTA AAACGTTTAT TGATACTTCA | 1080 |
| GTTGCAAAGG ATGTTGATAA TTCTACACAG GCGAACCATA AAAAGAAGAA AAGTAAATCT | 1140 |
| AAGCCGAGGA AAACGGAACC GGAAGATGAA ATTGAAAAAG CTTTGAAAGA AATTCAAGCT | 1200 |
| AGTGAGAAAA AACTTACGAA GTCTATCGAT AACATTGTGA ATAAATTTAA TACACCACTT | 1260 |

GCTAGTGTTA AAGCCGATGA TTCCAATTCT ACCAAGGATA ATGTACCAGC AAAGAAGAAA 1320  
 AAACCTTCGA AGTCATCTGT TTCTTTACCT GAGAATGTAG TACAAAATCT ATTGATACTA 1380  
 5 ACA 1383

## (2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 1758 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 1...1758

(ix) FEATURE:  
 (A) NAME/KEY: W = A or T  
 (B) LOCATION: 1136

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

|    |   |     |
|----|---|-----|
| 30 | CTA GAG ATG GCT AAA TTT CTG ACG GAA ACA TTA GAC GAC ATG ACT CTA | 48  |
|    | Leu Glu Met Ala Lys Phe Leu Thr Glu Thr Leu Asp Asp Met Thr Leu |     |
|    | 1 5 10 15   |     |
| 35 | CAA CAC AAA GAT CAC AGA TCA GAA TTG GCT AAA GAG TTT TCA ATT TGG | 96  |
|    | Gln His Lys Asp His Arg Ser Glu Leu Ala Lys Glu Phe Ser Ile Trp |     |
|    | 20 25 30  |     |
| 40 | TTT ACG AAA ATG AGA CAG TCT GGC GCT CAA GCC AGT AAC GAA GAA ATC | 144 |
|    | Phe Thr Lys Met Arg Gln Ser Gly Ala Gln Ala Ser Asn Glu Glu Ile |     |
|    | 35 40 45  |     |
| 45 | ATG AAA TTT TCA AAA TTG TTT GAA GAT GAA ATC ACT CTT GAC TCG CTG | 192 |
|    | Met Lys Phe Ser Lys Leu Phe Glu Asp Glu Ile Thr Leu Asp Ser Leu |     |
|    | 50 55 60  |     |
| 50 | GCG AGG CCG CAA CTT GTT GCT TTG TGC AGG GTA CTA GAA ATC AGT ACT | 240 |
|    | Ala Arg Pro Gln Leu Val Ala Leu Cys Arg Val Leu Glu Ile Ser Thr |     |
|    | 65 70 75 80   |     |
| 55 | TTA GGA ACA ACA AAT TTC TTA AGG TTT CAA CTG CGA ATG AAA CTG CGT | 288 |
|    | Leu Gly Thr Thr Asn Phe Leu Arg Phe Gln Leu Arg Met Lys Leu Arg |     |
|    | 85 90 95  |     |
| 60 | TCA TTA GCT GCT GAT GAT AAA ATG ATT CAA AAA GAA GGC ATA GTT TCT | 336 |
|    | Ser Leu Ala Ala Asp Asp Lys Met Ile Gln Lys Glu Gly Ile Val Ser |     |
|    | 100 105 110   |     |
| 65 | ATG ACT TAT TCG GAG GTG CAA CAG GCC TGC AGA GCT CGT GGA ATG CGA | 384 |
|    | Met Thr Tyr Ser Glu Val Gln Gln Ala Cys Arg Ala Arg Gly Met Arg |     |
|    | 115 120 125   |     |
|    | GCT TAT GGT ATG CCT GAA CAT AGG TTG AGG AGG CAA TTG GAA GAC TGG | 432 |
|    | Ala Tyr Gly Met Pro Glu His Arg Leu Arg Arg Gln Leu Glu Asp Trp |     |
|    | 130 135 140   |     |
|    | ATT AAT TTA AGC TTG AAT GAA AAG GTT CCA CCA TCA TTA TTG CTT TTG | 480 |
|    | Ile Asn Leu Ser Leu Asn Glu Lys Val Pro Ser Leu Leu Leu Leu     |     |
|    | 145 150 155 160   |     |

|    |   |      |
|----|---|------|
|    | TCA AGG GCG CTG ATG TTG CCC GAG AAT GTT CCA GTG TCT GAT AAA CTT     | 528  |
|    | Ser Arg Ala Leu Met Leu Pro Glu Asn Val Pro Val Ser Asp Lys Leu     |      |
|    | 165 170 175   |      |
| 5  | AAA GCA ACA ATA AAT GCT CTT CCT GAA ACT ATT GTA ACT CAG ACA AAG     | 576  |
|    | Lys Ala Thr Ile Asn Ala Leu Pro Glu Thr Ile Val Thr Gln Thr Lys     |      |
|    | 180 185 190   |      |
| 10 | GCT GCT ATT GGA GAA AGA GAA GGA AAG ATT GAC AAT AAG ACC AAA ATT     | 624  |
|    | Ala Ala Ile Gly Glu Arg Glu Gly Lys Ile Asp Asn Lys Thr Lys Ile     |      |
|    | 195 200 205   |      |
| 15 | GAG GTC ATC AAA GAG GAA GAA CGC AAA ATT CGC GAA GAG CGC CAA GAA     | 672  |
|    | Glu Val Ile Lys Glu Glu Glu Arg Lys Ile Arg Glu Glu Arg Gln Glu     |      |
|    | 210 215 220   |      |
| 20 | GCA CGT GAG GAA GAG GAA CAA CGC AAG CAA GCC GAA CTT GCT CTT AAT     | 720  |
|    | Ala Arg Glu Glu Glu Glu Gln Arg Lys Gln Ala Glu Leu Ala Leu Asn     |      |
|    | 225 230 235 240   |      |
| 25 | GCC AGT TCT GCA GCA GCT GAG GCC TCT TCA GCT CAG GAA CTT TTG ATA     | 768  |
|    | Ala Ser Ser Ala Ala Ala Glu Ala Ser Ser Ala Gln Glu Leu Leu Ile     |      |
|    | 245 250 255   |      |
| 30 | GAT ACA GCT CCT GTA ATA GAT GCA GAA AAG ACA CCA AAG GTG GCA ACA     | 816  |
|    | Asp Thr Ala Pro Val Ile Asp Ala Glu Lys Thr Pro Lys Val Ala Thr     |      |
|    | 260 265 270   |      |
| 35 | TCA CCT GTT GAA TCA CCA TTG GCA CCA CCA GAA GTT CTG ATT ATG GGT     | 864  |
|    | Ser Pro Val Glu Ser Pro Leu Ala Pro Pro Glu Val Leu Ile Met Gly     |      |
|    | 275 280 285   |      |
| 40 | GCT CCT AAA ACA CCT GTT GCA ACC GAA GTG GAT AAG AAT GCT GAT GAG     | 912  |
|    | Ala Pro Lys Thr Pro Val Ala Thr Glu Val Asp Lys Asn Ala Asp Glu     |      |
|    | 290 295 300   |      |
| 45 | GTG GAA TTC ACC AAG AAA GAT CTT GAG GTT GTT GAA GAT GCA TTG GAT     | 960  |
|    | Val Glu Phe Thr Lys Lys Asp Leu Glu Val Val Glu Asp Ala Leu Asp     |      |
|    | 305 310 315 320   |      |
| 50 | ACA CTA TCG AAA GAC AAA AAT AAT TTG GTG ATT GAA AAG GAA GTT ATT     | 1008 |
|    | Thr Leu Ser Lys Asp Lys Lys Asn Asn Leu Val Ile Glu Lys Glu Val Ile |      |
|    | 325 330 335   |      |
| 55 | AAA GAC ATT AAG GAA GAA ATT GCT GAT TAC CAA GAA GAT GAT GAA GAA     | 1056 |
|    | Lys Asp Ile Lys Glu Glu Ile Ala Asp Tyr Gln Glu Asp Val Glu Glu     |      |
|    | 340 345 350   |      |
| 60 | TTG AAA GAA GCC ATA GTT GCT GCT GAG AAA CCA AAG GAT GAG ATA AAA     | 1104 |
|    | Leu Lys Glu Ala Ile Val Ala Ala Glu Lys Pro Lys Asp Glu Ile Lys     |      |
|    | 355 360 365   |      |
| 65 | GAA ACT AAA GGA GCT CAA CGA TTG TTG AAG AWG GTT AAC AAG ATG ATA     | 1152 |
|    | Glu Thr Lys Gly Ala Gln Arg Leu Leu Lys Xaa Val Asn Lys Met Ile     |      |
|    | 370 375 380   |      |
| 70 | ACG AAA ATG GAT ACT GTT GTA CAA GAA ATT GAA AGC AAA GAA TCT GAG     | 1200 |
|    | Thr Lys Met Asp Thr Val Val Gln Glu Ile Glu Ser Lys Glu Ser Glu     |      |
|    | 385 390 395 400   |      |
| 75 | AAG AAA GCC AAA ACA TTG CCA CTT GAA GCT CCT AGG AGC GCT ACT GAA     | 1248 |
|    | Lys Lys Ala Lys Thr Leu Pro Leu Glu Ala Pro Arg Ser Ala Thr Glu     |      |
|    | 405 410 415   |      |
| 80 | ACT CAA GAA TTA GAT GTA AGG AAA GAA AGA GGA GAG ATT TTA ATT GAC     | 1296 |
|    | Thr Gln Glu Leu Asp Val Arg Lys Glu Arg Gly Glu Ile Leu Ile Asp     |      |
|    | 420 425 430   |      |
| 85 | GAA TTA ATG GAC GCT ATT AAG AAA GTT AAA AAT GTG CCA GAC GAA AAT     | 1344 |

Glu Leu Met Asp Ala Ile Lys Lys Val Lys Asn Val Pro Asp Glu Asn  
 435 440 445

5 CGC TTG AAA TTA ATT GAG AAC ATT TTG GGC AGG ATC GAT ACT GAC AAA 1392  
 Arg Leu Lys Leu Ile Glu Asn Ile Leu Gly Arg Ile Asp Thr Asp Lys  
 450 455 460

10 GAT AGG CAT ATC AAA GTT GAA GAT GTA TTG AAG GTT ATT GAC ATT GTG 1440  
 Asp Arg His Ile Lys Val Glu Asp Val Leu Lys Val Ile Asp Ile Val  
 465 470 475 480

15 GAA AAA GAA GAT GGT ATC ATG AGT ACA AAA CAA TTA GAT GAG TTG GTT 1488  
 Glu Lys Glu Asp Gly Ile Met Ser Thr Lys Gln Leu Asp Glu Leu Val  
 485 490 495

20 CAG CTT TTG AAA AAG GAG GAA GTT ATT GAA TTG GAA GAA AAG AAA GAA 1536  
 Gln Leu Leu Lys Lys Glu Glu Val Ile Glu Leu Glu Glu Lys Lys Glu  
 500 505 510

25 AAG CAA GAG TCT CAA CAG AAA AGT TTT GTA CCA CCA AGT GAA ACT TTG 1584  
 Lys Gln Glu Ser Gln Gln Lys Ser Phe Val Pro Pro Ser Glu Thr Leu  
 515 520 525

30 CAT CTT GAA TCA TCA CAG CAG AAG AGT ACA GTT CCT AGC TCG GGA CAT 1632  
 His Leu Glu Ser Ser Gln Gln Lys Ser Thr Val Pro Ser Ser Gly His  
 530 535 540

35 GAA GCT AAG GTG TCC GAA GAT GAC TTA AAT GTT AAA AAT AAA AAT TTG 1680  
 Glu Ala Lys Val Ser Glu Asp Asp Leu Asn Val Lys Asn Lys Asn Leu  
 545 550 555 560

40 GAA GAA TCG ACC AAA ACT GAA TGT GGA GCA ATT GAC GAA GAG CAC AGA 1728  
 Glu Glu Ser Thr Lys Thr Glu Cys Gly Ala Ile Asp Glu Glu His Arg  
 565 570 575

45 AGA GAG CAT TGC CAG TAC CCA GAC ATT ACA 1758  
 Arg Glu His Cys Gln Tyr Pro Asp Ile Thr  
 580 585

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 586 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Leu Glu Met Ala Lys Phe Leu Thr Glu Thr Leu Asp Asp Met Thr Leu  
 1 5 10 15

55 Gln His Lys Asp His Arg Ser Glu Leu Ala Lys Glu Phe Ser Ile Trp  
 20 25 30

60 Phe Thr Lys Met Arg Gln Ser Gly Ala Gln Ala Ser Asn Glu Glu Ile  
 35 40 45

Met Lys Phe Ser Lys Leu Phe Glu Asp Glu Ile Thr Leu Asp Ser Leu  
 50 55 60

65 Ala Arg Pro Gln Leu Val Ala Leu Cys Arg Val Leu Glu Ile Ser Thr  
 65 70 75 80

Leu Gly Thr Thr Asn Phe Leu Arg Phe Gln Leu Arg Met Lys Leu Arg  
 85 90 95



Ser Leu Ala Ala Asp Asp Lys Met Ile Gln Lys Glu Gly Ile Val Ser  
 100 105 110  
 5 Met Thr Tyr Ser Glu Val Gln Gln Ala Cys Arg Ala Arg Gly Met Arg  
 115 120 125  
 Ala Tyr Gly Met Pro Glu His Arg Leu Arg Arg Gln Leu Glu Asp Trp  
 130 135 140  
 10 Ile Asn Leu Ser Leu Asn Glu Lys Val Pro Pro Ser Leu Leu Leu Leu  
 145 150 155 160  
 Ser Arg Ala Leu Met Leu Pro Glu Asn Val Pro Val Ser Asp Lys Leu  
 165 170 175  
 15 Lys Ala Thr Ile Asn Ala Leu Pro Glu Thr Ile Val Thr Gln Thr Lys  
 180 185 190  
 20 Ala Ala Ile Gly Glu Arg Glu Gly Lys Ile Asp Asn Lys Thr Lys Ile  
 195 200 205  
 Glu Val Ile Lys Glu Glu Glu Arg Lys Ile Arg Glu Glu Arg Gln Glu  
 210 215 220  
 25 Ala Arg Glu Glu Glu Glu Gln Arg Lys Gln Ala Glu Leu Ala Leu Asn  
 225 230 235 240  
 Ala Ser Ser Ala Ala Ala Glu Ala Ser Ser Ala Gln Glu Leu Leu Ile  
 245 250 255  
 30 Asp Thr Ala Pro Val Ile Asp Ala Glu Lys Thr Pro Lys Val Ala Thr  
 260 265 270  
 35 Ser Pro Val Glu Ser Pro Leu Ala Pro Pro Glu Val Leu Ile Met Gly  
 275 280 285  
 Ala Pro Lys Thr Pro Val Ala Thr Glu Val Asp Lys Asn Ala Asp Glu  
 290 295 300  
 40 Val Glu Phe Thr Lys Lys Asp Leu Glu Val Val Glu Asp Ala Leu Asp  
 305 310 315 320  
 Thr Leu Ser Lys Asp Lys Asn Asn Leu Val Ile Glu Lys Glu Val Ile  
 325 330 335  
 45 Lys Asp Ile Lys Glu Glu Ile Ala Asp Tyr Gln Glu Asp Val Glu Glu  
 340 345 350  
 50 Leu Lys Glu Ala Ile Val Ala Ala Glu Lys Pro Lys Asp Glu Ile Lys  
 355 360 365  
 Glu Thr Lys Gly Ala Gln Arg Leu Leu Lys Xaa Val Asn Lys Met Ile  
 370 375 380  
 55 Thr Lys Met Asp Thr Val Val Gln Glu Ile Glu Ser Lys Glu Ser Glu  
 385 390 395 400  
 Lys Lys Ala Lys Thr Leu Pro Leu Glu Ala Pro Arg Ser Ala Thr Glu  
 405 410 415  
 60 Thr Gln Glu Leu Asp Val Arg Lys Glu Arg Gly Glu Ile Leu Ile Asp  
 420 425 430  
 65 Glu Leu Met Asp Ala Ile Lys Lys Val Lys Asn Val Pro Asp Glu Asn  
 435 440 445  
 Arg Leu Lys Leu Ile Glu Asn Ile Leu Gly Arg Ile Asp Thr Asp Lys  
 450 455 460

Asp Arg His Ile Lys Val Glu Asp Val Leu Lys Val Ile Asp Ile Val  
465 470 475 480

Glu Lys Glu Asp Gly Ile Met Ser Thr Lys Gln Leu Asp Glu Leu Val  
485 490 495

Gln Leu Leu Lys Lys Glu Glu Val Ile Glu Leu Glu Glu Lys Lys Glu  
500 505 510

Lys Gln Glu Ser Gln Gln Lys Ser Phe Val Pro Pro Ser Glu Thr Leu  
515 520 525

His Leu Glu Ser Ser Gln Gln Lys Ser Thr Val Pro Ser Ser Gly His  
530 535 540

Glu Ala Lys Val Ser Glu Asp Asp Leu Asn Val Lys Asn Lys Asn Leu  
545 550 555 560

Glu Glu Ser Thr Lys Thr Glu Cys Gly Ala Ile Asp Glu Glu His Arg  
565 570 575

Arg Glu His Cys Gln Tyr Pro Asp Ile Thr  
580 585

(2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 293 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

|  |     |
|--|-----|
| CCCCGGGCTGC AGGAATTCGG CACGAGATGA GAATGGAAAT GTGATTAGCT ATACTGATGA | 60  |
| AAATGGAAAC ATTATCAGTA CTACTGATGA GAATGGAAAT GTGATTAGCA TTACTGATGA  | 120 |
| AAATGGAAAT GTGATTAGCA TTACTGATGA AAATGGAAAC ATTATCAGTA CTACTGATGA  | 180 |
| GAATGGAAAT GTGATTAGCA TTACTGATGA AAATGGAAAT GTGATTAGCA TTACTGATGA  | 240 |
| AAATGGAAAC ATTATTAGTA CTACTGATGA GAATGGAAAT GTGATTAGCA ATA         | 293 |

(2) INFORMATION FOR SEQ ID NO:32:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 335 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

|   |     |
|---|-----|
| TTGGAAACAG CTATGACCAT GATTACCCCA AGCTCGAAAG TTAAVCCCTC ACTHARAGGG | 60  |
| GAACAAAAGT CTGGAGCTCC ACCCGCGGAT GCGGCCGCB TCTAGAACCT AGTGGACTCC  | 120 |
| CCCGGSGCTG CAGGAATTCG GGCACGAGCT CCAGCTAGCC ATATACATTC ATCCAAAATG | 180 |
| AAGTTGSAAT GTGTCCTACC CGGCAACGGG ATGCCAGAAA TTGKTCGAA ATKTGTGGAC  | 240 |
| GAGCACAAGC TTCGTGTCTK TCTATGAAAA ACGTATGGGA GCAGAAGTCG AGGGCCGACA | 300 |

TCCTCGGCGA TGAATGGARA GGTATGTGC TCCGA

335

## (2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 396 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

ATAGCTTTTA ATATTTTAA TTGATGTATT GCTCAATGGT GATTCTGTT TATTAACTG 60  
 AGTTACCAAT ATGCTCGCTT CAATAGACAT AGCAAATGAA AGCATTCCGT ATCCTCAAGC 120  
 GTTACCAAAC TAACATTAAG GAGTTAAATA AATGTTGTTT CCAATAAATA TAATGGGAAA 180  
 AACATTTAAT ATTTGTTCCA ATTTGTATTT ATTTTACTA CAATTATATA CAATAAAATA 240  
 TTTTATATA TATTTTATAA AGTTTATGAT GCAGGAGAGA AAATAATGTT AAGAATATAG 300  
 GTAATGTGTA TATATAAATG TTTGACAAGC ATGTTCTAGT TAAATAATAA ATACAATGTT 360  
 AAATCTACTT AAAAAAAAAA AAAAAAAAAA AAAAAA 396

## (2) INFORMATION FOR SEQ ID NO:34:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 285 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GGAAAGCGAA GAATGAAAAG GGGAAACAAA AAAAGAAAAG ACGAAGGAGT GGAGAGATAA 60  
 AACGGAGGCA AAGAAGAAAA TGAGGATGCA AAAGAAAGGT AATAAAGAG ATGAAAAGAA 120  
 GGAAAAAGGA AATAAGAAAAG AAAGAGTGAG GGAAAAATAA AGACAGAGGC GAAGCAAAAA 180  
 AGGAGGAGAA ATAGAGATTA AAAAGAAAT ACAGCGAAGA AACCAGGAAA GCGATAAAGA 240  
 AAAAAAAGA AAAAAAGAGA GCAGTGAAAA AAAAAAAAAA AAAAAA 285

## (2) INFORMATION FOR SEQ ID NO:35:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 228 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CAGATATTTA CTAAAYATTG TGAAAYAAAT CATTTCAAA ATGGTSTCCA AAGTGTGTTGT 60  
 TGCTCTTGCC ATCAATGGCT TTATAGGGGG CTSCACAAGY CTTTTTTCGA ACAAGATGMC 120  
 5 GTCTTAGATA ASATSGTAGA TRACATCTCT GRCTSMATAT GAGAACARCA TTGSMAGAAT 180  
 TAGCCAAGGR TNGCRAAATT GATATGMTTS CYGCTGTAAT TCGAAAAA 228

## (2) INFORMATION FOR SEQ ID NO:36:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 339 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 1..339

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CTT CGT GTC AAC CGC TGG GTC AGA CCT GTT ATT GCT ATG CAC CCA ACC 48  
 Leu Arg Val Asn Arg Trp Val Arg Pro Val Ile Ala Met His Pro Thr  
 1 5 10 15  
 30 ATG ACT CTT GCT GAA CGT CTC GGC AAA AAA GCT TTG CGC GAC CAA TAT 96  
 Met Thr Leu Ala Glu Arg Leu Gly Lys Lys Ala Leu Arg Asp Gln Tyr  
 20 25 30  
 35 GCT CCC GTT TGC TCC ATT GGA CAA CGT AAC ATC AAC ACC TTT GAC AAC 144  
 Ala Pro Val Cys Ser Ile Gly Gln Arg Asn Ile Asn Thr Phe Asp Asn  
 35 40 45  
 40 ATG ACC TTC CCC GCT CAA TTC GGA AAA TGC TGG CAC GCT TTG TTG CAA 192  
 Met Thr Phe Pro Ala Gln Phe Gly Lys Cys Trp His Ala Leu Leu Gln  
 50 55 60  
 45 ACT GTT CCC CAA AAG TAT TCC GAA GAA CGT GAA TAC AGC GAA GAA CAA 240  
 Thr Val Pro Gln Lys Tyr Ser Glu Glu Arg Glu Tyr Ser Glu Glu Gln  
 65 70 75 80  
 288 CAA TAC GAC CGT CAA ATG TCC GTC CTC GTT CGT GAA AAC GGC GAA GAA 288  
 Gln Tyr Asp Arg Gln Met Ser Val Leu Val Arg Glu Asn Gly Glu Glu  
 85 90 95  
 50  
 336 AAA AGA CGT TAT GAT TGT CTT GGG CAA CCG TTA CAA CAA TTG AAT TGC 336  
 Lys Arg Arg Tyr Asp Cys Leu Gly Gln Pro Leu Gln Gln Leu Asn Cys  
 100 105 110  
 AAT 339  
 Asn

## (2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 113 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Leu Arg Val Asn Arg Trp Val Arg Pro Val Ile Ala Met His Pro Thr  
 1 5 10 15  
 Met Thr Leu Ala Glu Arg Leu Gly Lys Lys Ala Leu Arg Asp Gln Tyr  
 20 25 30  
 Ala Pro Val Cys Ser Ile Gly Gln Arg Asn Ile Asn Thr Phe Asp Asn  
 35 40 45  
 Met Thr Phe Pro Ala Gln Phe Gly Lys Cys Trp His Ala Leu Leu Gln  
 50 55 60  
 Thr Val Pro Gln Lys Tyr Ser Glu Glu Arg Glu Tyr Ser Glu Glu Gln  
 65 70 75 80  
 Gln Tyr Asp Arg Gln Met Ser Val Leu Val Arg Glu Asn Gly Glu Glu  
 85 90 95  
 Lys Arg Arg Tyr Asp Cys Leu Gly Gln Pro Leu Gln Gln Leu Asn Cys  
 100 105 110  
 Asn

## (2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 493 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..390

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TCC AGC TCC TCC AGC TCC AGC AGT GAC TCT TCC AGC TCC AGC AGC TCT 48  
 Ser Ser Ser Ser Ser Ser Ser Ser Asp Ser Ser Ser Ser Ser Ser Ser  
 1 5 10 15  
 TCC TCT TCC AGC TCC AGC AGC TCC TCT TCT GAA TCT TCC GAA GAA AAA 96  
 Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Glu Ser Ser Glu Glu Lys  
 20 25 30  
 ACC TCC CAC AAA AAA TCC GAA AAG AAG GAA CAC AAA TCC TGC TCC ATC 144  
 Thr Ser His Lys Lys Ser Glu Lys Lys Glu His Lys Ser Cys Ser Ile  
 35 40 45  
 AAG AAG CAA GTA CAA TTC GTA GAA AAA GAC GGT AAA CTC TGC TTC AGC 192  
 Lys Lys Gln Val Gln Phe Val Glu Lys Asp Gly Lys Leu Cys Phe Ser  
 50 55 60  
 ATC CGT CCC TTG GCC GCT TGC CAA AAA CAC TGC AAA GCC ACT GAA ACC 240  
 Ile Arg Pro Leu Ala Ala Cys Gln Lys His Cys Lys Ala Thr Glu Thr  
 65 70 75 80  
 ACT CAA ATG GAA GTC GAA GTA TAC TGC CCC TCT GGC AGC CTT GCT GAA 288  
 Thr Gln Met Glu Val Glu Val Tyr Cys Pro Ser Gly Ser Leu Ala Glu  
 85 90 95  
 CTT TAC AAA CAA AAG ATC CTT AAG GGA GCC AAC CCC GAC TTG AGC GAC 336  
 Leu Tyr Lys Gln Lys Ile Leu Lys Gly Ala Asn Pro Asp Leu Ser Asp  
 100 105 110

AAG ACT CCT TCC AGA ATC TTG AAA TTC AAG GTT CCC AAA GCT TGC ACC 384  
 Lys Thr Pro Ser Arg Ile Leu Lys Phe Lys Val Pro Lys Ala Cys Thr  
 115 120 125

5 GCT TAC TAAATCTGAA ATAAATTACA TGGATTAGTT CATTCTGAT GTAGTGAAT 440  
 Ala Tyr  
 130

10 TAGTTCGATA ATAAATTATT CAATGAGCAT TTAAAAAAAA AAAAAAAAAA AAC 493

(2) INFORMATION FOR SEQ ID NO:39:

15 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 130 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

25 Ser Ser Ser Ser Ser Ser Ser Ser Asp Ser Ser Ser Ser Ser Ser Ser  
 1 5 10 15  
 Ser Ser Ser Ser Ser Ser Ser Ser Ser Glu Ser Ser Glu Glu Lys  
 20 25 30  
 Thr Ser His Lys Lys Ser Glu Lys Lys Glu His Lys Ser Cys Ser Ile  
 35 40 45  
 Lys Lys Gln Val Gln Phe Val Glu Lys Asp Gly Lys Leu Cys Phe Ser  
 50 55 60  
 35 Ile Arg Pro Leu Ala Ala Cys Gln Lys His Cys Lys Ala Thr Glu Thr  
 65 70 75 80  
 Thr Gln Met Glu Val Glu Val Tyr Cys Pro Ser Gly Ser Leu Ala Glu  
 85 90 95  
 40 Leu Tyr Lys Gln Lys Ile Leu Lys Gly Ala Asn Pro Asp Leu Ser Asp  
 100 105 110  
 45 Lys Thr Pro Ser Arg Ile Leu Lys Phe Lys Val Pro Lys Ala Cys Thr  
 115 120 125  
 Ala Tyr  
 130

50 (2) INFORMATION FOR SEQ ID NO:40:

55 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 306 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

60 (ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GTAGTGCCAT CATTCTGAAA CSTTGTGACG GTKGGGCGCT GTATWGGTGC TGCCTGGAAA 60  
 65 TTGCATCGAT GCACTWCCGT GTCGGGCGCA WATAGTGCKK TGGSCCCTGT CTGMTTATAG 120  
 ACATTCAGGG CGCSGGS AKT AGCCATGTTC ATGGCTCMCA AWMTGCATTC ACAGTGGGGT 180  
 CACATTTCAG TCGCATGATT KMTCAARTTA GTATMWGADA TATATTTTTA TCATACTAAG 240

TAGTGAGCDA ATAACACGCG ARWWACRAAC ACCGAATATC TTKAGTTTTT GCACAGATAT 300  
KTGTAA 306

5

## (2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 490 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

10

## (ii) MOLECULE TYPE: cDNA

15

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

ACCGGATACG TTGCCAATGA CTACGTCACC ACCAATGTTG TTTCCACTCC AGTTACTGGA 60  
TACACCACCG GACATCTTGC TAATGACTAC GTCACCACCA ATGTTGTATC CACTCCAGTT 120  
ACTGGATACA CCACCGGACA TCTTGCCAAT GACTACGTCA CCACCAACGT AGTTTCCGCA 180  
CCAGTCACCA CTGGATACAC CACTGGCTAT ACCACCGGTA ATGTCGGATA CACCACCGGA 240  
GTTACTGGTT ACACCAACGG AGTTAGTGGA TATACCAATG GACTTAATGG TTATACCACT 300  
GGTAGCTATG TCAGCTCCCC AGGATACACT TCTTCTGGAC TTGTCAACGT TTTCTAGATT 360  
TATGATTTTC TCTGCCCTCA ATGATGATGA CCACACTTTT TACTTTTTAT GATATTTGGA 420  
AAAAATAAAT AACTGGAAGA ATATATAATA ATTTCAAAAT AAAAAAAAAA AAAAAAAAAA 480  
CTCGAGGGGG 490

35

## (2) INFORMATION FOR SEQ ID NO:42:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 616 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

40

## (ii) MOLECULE TYPE: cDNA

45

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

AAAAATCGA AAGAAGGCGT AAAACCAAAA TGGGCACAGA AGGATATTCG GGATTTTAGT 60  
GATGCCGACA TGGAGAGGTT ACTGGATCAA TGGGAAGAAG ATGAAGACCC CCTTCCAGAA 120  
GACGAATTGC CCGAACATCT CAGACCTGAT CCAAAGATCG ACATAAGCAA CATCGATATG 180  
AGCAATCCCB AAAACATACT AAAGGCTTCC AAAAAAGGCA AGACTTTGAT GGCATTCGTA 240  
CAAGTCAGTG GAAATCCAAC ACAAGAAGAA GCCGAAACCA TCACTAAATT GTGGCAAGGC 300  
AGTCTATGGA ATAGTCATAT ACAAGCCGAA AGATATATGG TTAGCGATGA CAGGGCTATA 360  
TTTATGTTTA AAGATGGTTC TCAAGCTTGG CTGCTAAAG ACTTTTLAGT GGAACAAGAA 420  
AGGTGTAAAG ATGTTACAA TGAATAATAA ATATATCCTG GTAAATATTC TTCGACTAAA 480  
GAAGAATTAT AATATAATAT ATTATAATTA TAATCTATAA AATAGATTG AAATTCTACA 540  
TTCATGATCT ACTATGTATG ATATTAATTT ATTAAAAATA ATGTTTTTTC AAGTAAAAAA 600  
AAAAAAAAAA AAAAAA 616

65

## (2) INFORMATION FOR SEQ ID NO:43:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 475 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CTCGTGC GGG ACAGATATAG GACCGGATTC GTTAATTGAT TTGAGTGAAG TGGCTTCTGG 60  
 TGGTTCTGAT ATTGACACAA AATTTTCCAA TTAAAAATA GATAAAAAGC CTGTTGCAAC 120  
 TTCACAACAA GGAATTGATG AATTTGATAT GTTTCACAA TCGAGAAACA TTTCTAGTGA 180  
 GGGATCAACC AGTGCTATGA AGGAAGGACA CGGTTTGGAC TTATTATCAA ATACACATAA 240  
 AAATGTACCA CCAACAATTC CACAAGCCGG ACAACTTCCA AGGGATTCTG AGTTTGATGA 300  
 AATTGCTGCT TGGCTTGATG AAAAGGTGA AGACAAAGCC CAAGTTCCCG AAGACAGTAT 360  
 TACAAGCAGT GAATTTGATA AATTCCTGGC AGAACGGGCA GCTGTTGCTG AACTTTGCC 420  
 AAATATTCCA CCGACTACAC AAAGTAATCA TTCAATATT GAAGCAAACG ATAAA 475

## (2) INFORMATION FOR SEQ ID NO:44:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 295 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CCGGCACGGG AGGTAGTGAC GAAAAATAAC GATACGGGAC TCATCCGAGG CCCCCTAATC 60  
 GGAATGAGTA CACTTTAAAT CCTTTAACGA GGATCTATTA GAGGGCCAGT CTGTGTGCCA 120  
 GCAGCCCGGG TAATTCCAGC TCTAATAGCG TATATTAAAG TTGTTGCGGT TAAAAAGCTC 180  
 GTAGTTGAAT CTGTGTCCCA CACTGTGGT TCACCGCTCG CGGTGTTCAA CTGGCATGTC 240  
 TGTGGGACGT CCTACCGGTG GGCTTAGCCC GTCAAAGGC GGCCCACTC AAAAT 295

## (2) INFORMATION FOR SEQ ID NO:45:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 372 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CTGACTAATC CCAGGACTCC TTTATCCTGT TTGCGCAATG TCGATACCCA TCTCACAATG 60  
 GTTAATGATT TATCGGCTAA ACAGAAGAGT CCTAAGAAGG TTGTTAAAGG TGTTTCTAGA 120  
 ATACCGACTT TTAGACCCAA GGCTATGAAT GCTGATGTTG AGAATTTTGA TTCGATGAGG 180



TGCGATGTTT GGRACAAAGA CACCAGTGTT GTTATATAAT TACTAAAGCA ATCCACATGT 240  
 AGCTAATTTT TTTTTCACAA TTTTATTGT AACTATGTGT ATTTATATGA ATTCTTGTGG 300  
 5 AATATAATTT TAAGTTTSTA AATGAAATAT AGATATTATT CTAAAAA AAAACAAAA 360  
 AAAAAA AA 372

## (2) INFORMATION FOR SEQ ID NO:46:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 252 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GGATTCGGCA CGAGAATTTA TTAAGCGCAT TATTGCAAG TGTAATTTGC TCCTTTAACG 60  
 CGGAAGTACA AAATCGAATC GTTGGTGGCA ATGATGTAAG TATTTCAAAA ATTGGGTGGC 120  
 25 AAGTATCTAT TCAAAGTAAT AACCAACATT TCTGTGGTGG TTCAATCATT GCTAAAGATT 180  
 GGGTACTGAC TTCTTCTCAA TCGCTCGTGG ACAAACAAAG TCCACCGAAG GATTAACTG 240  
 30 TTCGTGTTGG AA 252

## (2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 613 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

ATTCCTGCTG TTAATAGTAC TAATGCAGTA ATTGCTGCHA GCTGCTGCAQ AGAGGTTTTT 60  
 AAAATGGCAA CAAGTTGTTA CACCCACATG AACAACTACA TGGTATTCAA TGATACCGAT 120  
 GGGATTTATA CATATACTTA CGAAGCTGAA AGAAAACCTG ACTGTTTAGC TTGTTACAA 180  
 50 ATTCCAAAA CTATAGAAGT TTCTAATCCT GAAAATATGA CTCTCCAAGA CTTGATTACT 240  
 TTGTTGTGTG AAGGGGCTGA ATATCAAATG AAGAGCCCAG GTATTGTAGC CTCAATCGAA 300  
 55 GGCAAAAACA AAACCTTATA CATGTCAACA GTAGCAAGTA TAGAAGAAAA GACTAAACAG 360  
 AATCTAACAA AGTCTCTAAA AGAATTAAAT CTAGAAAATG GAATGGAAC TATGGTTGCA 420  
 GATGTGACGA CACCAAACAC AATATTACTT AAATTAAAAT ATAAGAATGT AATTGAAAC 480  
 60 GATGTTGAGA TGACTTGATA TTTACTTAAA AATGTTATCT TACAATAATT GATAATTTAT 540  
 ATTTAATACT TTTGGAACCT TGTATTTAAT GATAATAAAT TATTATAAGA ATTAAAAAA 600  
 65 AAAAAA AAA 613

## (2) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 538 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

- (ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 3..538

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

|    |   |     |
|----|---|-----|
| 15 | TT GAT ATT TGC TCT GTT GAG GGT GCC TTA GGA TTT TTA GTG GAA ATG  | 47  |
|    | Asp Ile Cys Ser Val Glu Gly Ala Leu Gly Phe Leu Val Glu Met     |     |
|    | 1 5 10 15   |     |
| 20 | TTA AAA TAT AAG GCC CCA AGT AAA ACT CTA GCT ATT GTA GAG AAT GCT | 95  |
|    | Leu Lys Tyr Lys Ala Pro Ser Lys Thr Leu Ala Ile Val Glu Asn Ala |     |
|    | 20 25 30  |     |
| 25 | GGT GGA ATA TTA CGA AAT GTA TCT AGT CAT ATA GCC CTT AGA GAG GAC | 143 |
|    | Gly Gly Ile Leu Arg Asn Val Ser Ser His Ile Ala Leu Arg Glu Asp |     |
|    | 35 40 45  |     |
| 30 | TAC AGA GAA ATA CTT CGA CAT CAT AAT TGC TTA ACA ATA TTA CTA CAA | 191 |
|    | Tyr Arg Glu Ile Leu Arg His His Asn Cys Leu Thr Ile Leu Leu Gln |     |
|    | 50 55 60  |     |
| 35 | CAA TTA AAA TCA CCA AGC CTC ATA ATT GTC AGT AAT GCT TGT GGG ACA | 239 |
|    | Gln Leu Lys Ser Pro Ser Leu Ile Ile Val Ser Asn Ala Cys Gly Thr |     |
|    | 65 70 75  |     |
| 40 | TTA TGG AAT TTA TCT GCT AGG AAT TCA ACA GAT CAA CAA TTT TTA TGG | 287 |
|    | Leu Trp Asn Leu Ser Ala Arg Asn Ser Thr Asp Gln Gln Phe Leu Trp |     |
|    | 80 85 90 95   |     |
| 45 | GAG AAT GGT GCT GTC CCT TTA TTA AGA AGT TTG ATA TAT TCT AAG CAT | 335 |
|    | Glu Asn Gly Ala Val Pro Leu Leu Arg Ser Leu Ile Tyr Ser Lys His |     |
|    | 100 105 110   |     |
| 50 | AAA ATG ATA TCT ATG GGA TCA AGT GCA GCT CTC AAA AAT TTG TTA AAT | 383 |
|    | Lys Met Ile Ser Met Gly Ser Ser Ala Ala Leu Lys Asn Leu Leu Asn |     |
|    | 115 120 125   |     |
| 55 | GCA AAA CCT GAG TGC ATC AAT TTC TTA AGT GAT TCT TCT TCT AAA GGA | 431 |
|    | Ala Lys Pro Glu Cys Ile Asn Phe Leu Ser Asp Ser Ser Ser Lys Gly |     |
|    | 130 135 140   |     |
| 60 | GTT CCA AAT CTA ACT ACA TTG GGT GTA AGA AAA CAA AAA TCT CTA CAT | 479 |
|    | Val Pro Asn Leu Thr Thr Leu Gly Val Arg Lys Gln Lys Ser Leu His |     |
|    | 145 150 155   |     |
| 65 | GAG TTA ATA GAT CAA AAT CTT TCA GAA ACT TGT GAT AAT ATA GAT AGT | 527 |
|    | Glu Leu Ile Asp Gln Asn Leu Ser Glu Thr Cys Asp Asn Ile Asp Ser |     |
|    | 160 165 170 175   |     |
| 70 | GTG GCC GCT AA  | 538 |
|    | Val Ala Ala   |     |

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 178 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

5 Asp Ile Cys Ser Val Glu Gly Ala Leu Gly Phe Leu Val Glu Met Leu  
1 5 10 15

Lys Tyr Lys Ala Pro Ser Lys Thr Leu Ala Ile Val Glu Asn Ala Gly  
20 25 30

10 Gly Ile Leu Arg Asn Val Ser Ser His Ile Ala Leu Arg Glu Asp Tyr  
35 40 45

Arg Glu Ile Leu Arg His His Asn Cys Leu Thr Ile Leu Leu Gln Gln  
15 50 55 60

Leu Lys Ser Pro Ser Leu Ile Ile Val Ser Asn Ala Cys Gly Thr Leu  
65 70 75 80

20 Trp Asn Leu Ser Ala Arg Asn Ser Thr Asp Gln Gln Phe Leu Trp Glu  
85 90 95

Asn Gly Ala Val Pro Leu Leu Arg Ser Leu Ile Tyr Ser Lys His Lys  
100 105 110

25 Met Ile Ser Met Gly Ser Ser Ala Ala Leu Lys Asn Leu Leu Asn Ala  
115 120 125

Lys Pro Glu Cys Ile Asn Phe Leu Ser Asp Ser Ser Ser Lys Gly Val  
30 130 135 140

Pro Asn Leu Thr Thr Leu Gly Val Arg Lys Gln Lys Ser Leu His Glu  
145 150 155 160

35 Leu Ile Asp Gln Asn Leu Ser Glu Thr Cys Asp Asn Ile Asp Ser Val  
165 170 175

Ala Ala

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 432 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS  
 (B) LOCATION: 1..388

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GTT CTT CTT AAA CAG TTG GAC TCT GGA TTG TTA CTT GTT ACA GGT CCC 48  
 Val Leu Leu Lys Gln Leu Asp Ser Gly Leu Leu Val Thr Gly Pro  
 1 5 10 15

60 TTC TTA ATC AAT GCA TGC CCA TTG CGT CGC ATT TCC CAA AAC TAT GTC 96  
 Phe Leu Ile Asn Ala Cys Pro Leu Arg Arg Ile Ser Gln Asn Tyr Val  
 20 25 30

65 ATT GCC ACC TCT ACC CGA TTA GAC GTT AGT GGA GTT AAA TTA CCA GAA 144  
 Ile Ala Thr Ser Thr Arg Leu Asp Val Ser Gly Val Lys Leu Pro Glu  
 35 40 45

CAC ATC AAT GAT GAT TAT TTC AAA AGG CAA AAG AAC AAG CGT GCA AAG 192

His Ile Asn Asp Asp Tyr Phe Lys Arg Gln Lys Asn Lys Arg Ala Lys  
 50 55 60  
 5 AAA GAG GAA GGT GAT ATT TTT GCT GCC AAG AAA GAG GCT TAT AAA CCA 240  
 Lys Glu Glu Gly Asp Ile Phe Ala Ala Lys Lys Glu Ala Tyr Lys Pro  
 65 70 75 80  
 10 ACT GAG CAA AGG AAG AAT GAC CAA AAG CTT GTA GAC AAA ATG GTT TTA 288  
 Thr Glu Gln Arg Lys Asn Asp Gln Lys Leu Val Asp Lys Met Val Leu  
 85 90 95  
 15 GGA GTA ATC AAG AAG CAC CCA GAC CAC AAA CTT TTG TAT ACA TAT TTG 336  
 Gly Val Ile Lys Lys His Pro Asp His Lys Leu Leu Tyr Thr Tyr Leu  
 100 105 110  
 20 TCA GCT ATG TTT GGT TTG AAA TCT TCC CAA TAT CCA CAT CGT ATG AAG 384  
 Ser Ala Met Phe Gly Leu Lys Ser Ser Gln Tyr Pro His Arg Met Lys  
 115 120 125  
 20 TTC T AAATACTATA TTCATAAAAT AAATTGAACT TCTCAAAAAA AAAA 432  
 Phe

## (2) INFORMATION FOR SEQ ID NO:51:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 129 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Val Leu Leu Lys Gln Leu Asp Ser Gly Leu Leu Leu Val Thr Gly Pro  
 1 5 10 15  
 Phe Leu Ile Asn Ala Cys Pro Leu Arg Arg Ile Ser Gln Asn Tyr Val  
 20 25 30  
 Ile Ala Thr Ser Thr Arg Leu Asp Val Ser Gly Val Lys Leu Pro Glu  
 35 40 45  
 45 His Ile Asn Asp Asp Tyr Phe Lys Arg Gln Lys Asn Lys Arg Ala Lys  
 50 55 60  
 Lys Glu Glu Gly Asp Ile Phe Ala Ala Lys Lys Glu Ala Tyr Lys Pro  
 65 70 75 80  
 50 Thr Glu Gln Arg Lys Asn Asp Gln Lys Leu Val Asp Lys Met Val Leu  
 85 90 95  
 55 Gly Val Ile Lys Lys His Pro Asp His Lys Leu Leu Tyr Thr Tyr Leu  
 100 105 110  
 Ser Ala Met Phe Gly Leu Lys Ser Ser Gln Tyr Pro His Arg Met Lys  
 115 120 125  
 60 Phe

## (2) INFORMATION FOR SEQ ID NO:52:

- 65 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 595 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 47..315

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```

5      TGGAAATTC AATTTTGT TTAACATTAA ATTTTTCAAA TCGAT ATG AAA TTT      55
          Met Lys Phe
          1
15     TTA CTG GCA ATT TGC GTG TTG TGT GTT TTA TTA AAT CAA GTA TCT ATG      103
          Leu Leu Ala Ile Cys Val Leu Cys Val Leu Leu Asn Gln Val Ser Met
          5          10          15
20     TCA AAA ATG GTC ACT GAA AAG TGT AAA TCG GGA GGA AAT AAT CCA AGT      151
          Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn Asn Pro Ser
          20          25          30          35
25     ACA AAA GAG GTG TCA ATA CCA TCT GGG AAG CTT ACT ATT GAA GAT TTT      199
          Thr Lys Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile Glu Asp Phe
          40          45          50
30     TGT ATT GGA AAT CAT CAA AGT TGC AAA ATA TTT TGC AAA AGT CAA TGT      247
          Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Cys Lys Ser Gln Cys
          55          60          65
35     GGA TTT GGA GGT GGT GCT TGT GGA AAC GGT GGT TCA ACA CGA CCA AAT      295
          Gly Phe Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr Arg Pro Asn
          70          75          80
40     CAA AAA CAC TGT TAT TGC GA ATAACCATAT TCCGGATGAA AGACCAAATT      345
          Gln Lys His Cys Tyr Cys
          85
45     GATATAAATT ACTAAAATTA TGCTAGATAG CAATCATAAA ATTTTGAAGT TTTCAATGAT      405
          CCTAACATGT TTTGCTCTCA ATTTATTTTA ACAGCAAATT GCTGGGAACT TACCGTACCG      465
          TAACAAAATG TTCAAGAAAT ACTGAATGTT TACAAATAGA TTATTATAAA TATTGTAACA      525
          TTGTCTAATA TTTATAAGAA TTATATAAAC TGAATTGCAA AAGTTGAAAA AAAAAAAAAA      585
          AAAAAAAAAA      595

```

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 89 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```

65     Met Lys Phe Leu Leu Ala Ile Cys Val Leu Cys Val Leu Leu Asn Gln
          1          5          10          15
          Val Ser Met Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn
          20          25          30

```

Asn Pro Ser Thr Lys Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile  
                   35                  40                  45

5 Glu Asp Phe Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Cys Lys  
           50                  55                  60

Ser Gln Cys Gly Phe Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr  
   65                  70                  75                  80

10 Arg Pro Asn Gln Lys His Cys Tyr Cys  
                   85

## (2) INFORMATION FOR SEQ ID NO:54:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 595 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

TTTTTTTTTT TTTTTTTTTT TTTCAACTT TTGCAATTCA GTTATATAA TTCTTATAAA 60  
 TATTAGACAA TGTTACAATA TTTATAATAA TCTATTGTA AACATTCAGT ATTCTTGAA 120  
 CATTTTGTTA CGGTACGGTA AGTCCCAGC AATTGCTGT TAAATAAAT TGGAGGCAAA 180  
 ACATGTTAGG ATCATTGAAA ACTTCAAAAT TTTATGATTG CTATCTAGCA TAATTTTAGT 240  
 AATTTATATC AATTGGTCT TTCATCCGGA ATATGTTAT TCGCAATAAC AGTGTTTTTG 300  
 ATTTGGTCGT GTTGAACCAC CGTTCCACA AGCACCACCT CCAAATCCAC ATTGACTTTT 360  
 GCAAAATATT TTGCAACTTT GATGATTTCC AATACAAAAA TCTCAATAG TAAGCTTCCC 420  
 AGATGGTATT GACACCTCTT TTGACTTGG ATTATTCCT CCCGATTAC ACTTTTCAGT 480  
 GACCATTTT GACATAGATA CTTGATTTAA TAAACACAC AACACGCAA TTGCCAGTAA 540  
 AAATTCATA TCGAATTGA AAAATTTAAT GTTAAACAA AATATTGAAT TTCCA 595

## (2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 270 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 1..270

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

ATG AAA TTT TTA CTG GCA ATT TGC GTG TTG TGT GTT TTA TTA AAT CAA 48  
 Met Lys Phe Leu Leu Ala Ile Cys Val Leu Cys Val Leu Leu Asn Gln  
   1                  5                  10                  15

GTA TCT ATG TCA AAA ATG GTC ACT GAA AAG TGT AAA TCG GGA GGA AAT 96  
 Val Ser Met Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn  
           20                  25                  30

AAT CCA AGT ACA AAA GAG GTG TCA ATA CCA TCT GGG AAG CTT ACT ATT 144  
 Asn Pro Ser Thr Lys Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile  
           35                          40                          45

5 GAA GAT TTT TGT ATT GGA AAT CAT CAA AGT TGC AAA ATA TTT TGC AAA 192  
 Glu Asp Phe Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Cys Lys  
           50                          55                          60

10 AGT CAA TGT GGA TTT GGA GGT GGT GCT TGT GGA AAC GGT GGT TCA ACA 240  
 Ser Gln Cys Gly Phe Gly Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr  
           65                          70                          75                          80

15 CGA CCA AAT CAA AAA CAC TGT TAT TGC GAA 270  
 Arg Pro Asn Gln Lys His Cys Tyr Cys Glu  
                                   85                                  90

## (2) INFORMATION FOR SEQ ID NO:56:

20 (i) SEQUENCE CHARACTERISTICS:  
       (A) LENGTH: 90 amino acids  
       (B) TYPE: amino acid  
       (D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

30 Met Lys Phe Leu Leu Ala Ile Cys Val Leu Cys Val Leu Leu Asn Gln  
       1                          5                          10                          15

Val Ser Met Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn  
                           20                          25                          30

35 Asn Pro Ser Thr Lys Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile  
           35                          40                          45

Glu Asp Phe Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Cys Lys  
           50                          55                          60

40 Ser Gln Cys Gly Phe Gly Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr  
           65                          70                          75                          80

45 Arg Pro Asn Gln Lys His Cys Tyr Cys Glu  
                                   85                                  90

## (2) INFORMATION FOR SEQ ID NO:57:

50 (i) SEQUENCE CHARACTERISTICS:  
       (A) LENGTH: 270 base pairs  
       (B) TYPE: nucleic acid  
       (C) STRANDEDNESS: single  
       (D) TOPOLOGY: linear

55 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

60 TTCGCAATAA CAGTGT TTTT GATTGGTTCG TGTTGAACCA CCGTTTCCAC AAGCACCACC 60

TCCAAATCCA CATTGACTTT TGCAAAATAT TTTGCAACTT TGATGATTTC CAATACAAAA 120

65 ATCTTCAATA GTAAGCTTCC CAGATGGTAT TGACACCTCT TTTGTACTTG GATTATTTCC 180

TCCCGATTTA CACTTTTCAG TGACCATTTT TGACATAGAT ACTTGATTTA ATAAACACA 240

CAACACGCAA ATTGCCAGTA AAAATTTTCAT 270

## (2) INFORMATION FOR SEQ ID NO:58:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 213 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

- (ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 1..213

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

TCA AAA ATG GTC ACT GAA AAG TGT AAA TCG GGA GGA AAT AAT CCA AGT 48  
 Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn Asn Pro Ser  
 1 5 10 15

ACA AAA GAG GTG TCA ATA CCA TCT GGG AAG CTT ACT ATT GAA GAT TTT 96  
 Thr Lys Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile Glu Asp Phe  
 20 25 30

TGT ATT GGA AAT CAT CAA AGT TGC AAA ATA TTT TGC AAA AGT CAA TGT 144  
 Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Cys Lys Ser Gln Cys  
 35 40 45

GGA TTT GGA GGT GGT GCT TGT GGA AAC GGT GGT TCA ACA CGA CCA AAT 192  
 Gly Phe Gly Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr Arg Pro Asn  
 50 55 60

CAA AAA CAC TGT TAT TGC GAA 213  
 Gln Lys His Cys Tyr Cys Glu  
 65 70

## (2) INFORMATION FOR SEQ ID NO:59:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 71 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn Asn Pro Ser  
 1 5 10 15

Thr Lys Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile Glu Asp Phe  
 20 25 30

Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Cys Lys Ser Gln Cys  
 35 40 45

Gly Phe Gly Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr Arg Pro Asn  
 50 55 60

Gln Lys His Cys Tyr Cys Glu  
 65 70

## (2) INFORMATION FOR SEQ ID NO:60:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 213 base pairs  
 (B) TYPE: nucleic acid



(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

TTCGCAATAA CAGTGTTTTT GATTGGTCG TGTTGAAQCA CCGTTCCAC AAGCACCACC 60  
TCCAAATCCA CATTGACTTT TGCAAAATAT TTTGCAACTT TGATGATTTC CAATACAAAA 120  
ATCTTCAATA GTAAGCTTCC CAGATGGTAT TGACACCTCT TTTGTACTTG GATTATTTCC 180  
TCCCGATTTA CACTTTTCAG TGACCATTTT TGA 213

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1007 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS  
(B) LOCATION: 1..465

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

TGG AAA GTT AAT AAA AAA TGT ACA TCA GGT GGA AAA AAT CAA GAT AGA 48  
Trp Lys Val Asn Lys Lys Cys Thr Ser Gly Gly Lys Asn Gln Asp Arg  
1 5 10 15  
AAA CTC GAT CAA ATA ATT CAA AAA GGC CAA CAA GTT AAA ATC CAA AAT 96  
Lys Leu Asp Gln Ile Ile Gln Lys Gly Gln Gln Val Lys Ile Gln Asn  
20 25 30  
ATT TGC AAA TTA ATA CGA GAT AAA CCA CAT ACA AAT CAA GAG AAA GAA 144  
Ile Cys Lys Leu Ile Arg Asp Lys Pro His Thr Asn Gln Glu Lys Glu  
35 40 45  
AAA TGT ATG AAA TTT TGC AAA AAA GTT TGC AAA GGT TAT AGA GGA GCT 192  
Lys Cys Met Lys Phe Cys Lys Lys Val Cys Lys Gly Tyr Arg Gly Ala  
50 55 60  
TGT GAT GGC AAT ATT TGC TAC TGC AGC AGG CCA AGT AAT TTA GGT CCT 240  
Cys Asp Gly Asn Ile Cys Tyr Cys Ser Arg Pro Ser Asn Leu Gly Pro  
65 70 75 80  
GAT TGG AAA GTA AGC AAA GAA TGC AAA GAT CCC AAT AAC AAA GAT TCT 288  
Asp Trp Lys Val Ser Lys Glu Cys Lys Asp Pro Asn Asn Lys Asp Ser  
85 90 95  
CGT CCT ACG GAA ATA GTT CCA TAT CGA CAA CAA TTA GCA AAT CCA AAT 336  
Arg Pro Thr Glu Ile Val Pro Tyr Arg Gln Gln Leu Ala Asn Pro Asn  
100 105 110  
ATT TGC AAA CTA AAA AAT TCA GAG ACC AAT GAA GAT TCC AAA TGC AAA 384  
Ile Cys Lys Leu Lys Asn Ser Glu Thr Asn Glu Asp Ser Lys Cys Lys  
115 120 125  
AAA CAT TGC AAA GAA AAA TGT CGT GGT GGA AAT GAT GCT GGA TGT GAT 432  
Lys His Cys Lys Glu Lys Cys Arg Gly Gly Asn Asp Ala Gly Cys Asp  
130 135 140

GGA AAC TTT TGT TAT TGT CGA CCA AAA AAT AAA TAATAATTAT AATAAATAAA 485  
 Gly Asn Phe Cys Tyr Cys Arg Pro Lys Asn Lys  
 145 150 155

5 TTGTTATAGT TATTAGTTAT CCCATCACAT ATTAGAAAAG TGGCTTATAA TTTATGAACA 545  
 ATATAACACA TAAATTAGTT GTGTAATTTT GAATGTTTTT TTCAAATATA AGGCGTTTTT 605  
 CTAGAATATC TTGATATTAG AAACAACTT AGATTATTTT GTTGTGTATA AAATATTCAA 665  
 10 ATACGTAAGT TATATTGAAC AAAGCATTTA GAAGCTACAT TAGATATACT AAATAAGTGC 725  
 AAAATTGCAT GGAAACCCCTT ACTGGATTTA CTACATATTT TCTTCCTAAA TATTGTCTTG 785  
 15 GTATTACTCT TATTATATAA AAATTAATAT AAAATTGTAG ACAGAGACGA ATTGGGGTAT 845  
 TGTATATATAT AAAAAAGTAG TGGATTATTT AATTCTAAAA AAGTTTGCAA AATGTTTCAT 905  
 ACATAATAAC CGAATATTTT CAAATATATA AATATTGTAA TGAATAAATG CGCATCTGTA 965  
 20 TGCTTAATAT AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AA 1007

## (2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 155 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

35 Trp Lys Val Asn Lys Lys Cys Thr Ser Gly Gly Lys Asn Gln Asp Arg  
 1 5 10 15  
 Lys Leu Asp Gln Ile Ile Gln Lys Gly Gln Gln Val Lys Ile Gln Asn  
 20 25 30  
 40 Ile Cys Lys Leu Ile Arg Asp Lys Pro His Thr Asn Gln Glu Lys Glu  
 35 40 45  
 Lys Cys Met Lys Phe Cys Lys Lys Val Cys Lys Gly Tyr Arg Gly Ala  
 50 55 60  
 Cys Asp Gly Asn Ile Cys Tyr Cys Ser Arg Pro Ser Asn Leu Gly Pro  
 65 70 75 80  
 50 Asp Trp Lys Val Ser Lys Glu Cys Lys Asp Pro Asn Asn Lys Asp Ser  
 85 90 95  
 Arg Pro Thr Glu Ile Val Pro Tyr Arg Gln Gln Leu Ala Asn Pro Asn  
 100 105 110  
 55 Ile Cys Lys Leu Lys Asn Ser Glu Thr Asn Glu Asp Ser Lys Cys Lys  
 115 120 125  
 Lys His Cys Lys Glu Lys Cys Arg Gly Gly Asn Asp Ala Gly Cys Asp  
 60 130 135 140  
 Gly Asn Phe Cys Tyr Cys Arg Pro Lys Asn Lys  
 145 150 155

65

## (2) INFORMATION FOR SEQ ID NO:63:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1007 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

```

TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTATATTAAG CATACAGATG CGCATTATT      60
CATTACAATA TTTATATATT TGAAATATT CGGTTATTAT GTATGAAACA TTTTGCAAAC      120
TTTTTTAGAA TTAATAATC CACTACTTTT TTATATATAA CAATACCCCA ATTCGTCTCT      180
GTCTACAATT TTATATTAAT TTTTATATAA TAAGAGTAAT ACCAAGACAA TATTTAGGAA      240
GAAAATATGT AGTAAATCCA GTAAGGGTTT CCATGCAATT TTGCACTTAT TTAGTATATC      300
TAATGTAGCT TCTAAATGCT TTGTTCAATA TAACCTACGT ATTTGAATAT TTTATACACA      360
ACAAAATAAT CTAAGTTAGT TTCTAATATC AAGATATTCT AGAAAAACGC CTTATATTTG      420
AAAAAACAT TCGAAATTAC ACAACTAATT TATGTGTTAT ATTGTCATA AATTATAAGC      480
CACTTTTCTA ATATGTGATG GGATAACTAA TAACTATAAC AATTTATTTA TTATAATTAT      540
TATTTATTTT TTGGTCGACA ATAACAAAAG TTTCCATCAC ATCCAGCATC ATTTCCACCA      600
CGACATTTTT CTTTGCAATG TTTTGTGCAT TTGGAATCTT CATTGGTCTC TGAATTTTTT      660
AGTTTGCAA TATTGGGAAT TGCTAATTGT TGTCGATATG GAACTATTTT CGTAGGACGA      720
GAATCTTTGT TATTGGGATC TTTGCATTCT TTGCTTACTT TCCAATCAGG ACCTAAATTA      780
CTTGGCCTGC TGCAGTAGCA AATATTGCCA TCACAAGCTC CTCTATAACC TTTGCAAAC      840
TTTTTGCAA ATTCATACA TTTTCTTTT TCTTGATTG TATGTGGTTT ATCTCGTATT      900
AATTTGCAA TATTTGGAT TTAACTTGT TGGCCTTTT GAATTATTTG ATCGAGTTT      960
CTATCTTGAT TTTTCCACC TGATGTACAT TTTTATTAA CTTTCCA      1007

```

## (2) INFORMATION FOR SEQ ID NO:64:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1205 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 4..1062

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

```

GCA GAA TTG AAA TTT GTG TTT GCG ACT GCA CGA GGT ATG TCA CAT ACA      48
Glu Leu Lys Phe Val Phe Ala Thr Ala Arg Gly Met Ser His Thr
  1             5             10             15

```

|    |   |     |
|----|---|-----|
|    | CCT TGT GAT TAT CCA GGC GGT CCA AAA ATT ACA CAC AAG TCT GAA GAT | 96  |
|    | Pro Cys Asp Tyr Pro Gly Gly Pro Lys Ile Thr His Lys Ser Glu Asp |     |
|    | 20 25 30  |     |
| 5  | TCA AGC CAA TTG ACA CCG GCA GGT CAA GAA GAG GCA TTA AAA ATT GGC | 144 |
|    | Ser Ser Gln Leu Thr Pro Ala Gly Gln Glu Glu Ala Leu Lys Ile Gly |     |
|    | 35 40 45  |     |
| 10 | AAA TTA TTA TCC GAA CAT TAC AGA ACT AAT TTA AAA GTT GAC AAA TGG | 192 |
|    | Lys Leu Leu Ser Glu His Tyr Arg Thr Asn Leu Lys Val Asp Lys Trp |     |
|    | 50 55 60  |     |
| 15 | GAT TCA AAT AAA AAT TAT TGG ACA TTA GCT AGT GCT ACG AGA AGA TCT | 240 |
|    | Asp Ser Asn Lys Asn Tyr Trp Thr Leu Ala Ser Ala Thr Arg Arg Ser |     |
|    | 65 70 75  |     |
| 20 | CAA GAA GGA GCG CTT ATC ATT GGT TCT GGT CTA GAA GAA AAG GAA AAG | 288 |
|    | Gln Glu Gly Ala Leu Ile Ile Gly Ser Gly Leu Glu Glu Lys Glu Lys |     |
|    | 80 85 90 95   |     |
| 25 | GCA GTT TGG ACA AAA GAG AAA GGA GAT AAA ACC ATA TTT TCT TCG TTT | 336 |
|    | Ala Val Trp Thr Lys Glu Lys Gly Asp Lys Thr Ile Phe Ser Ser Phe |     |
|    | 100 105 110   |     |
| 30 | GCA CAA CAG AAA ATA GCA GTA AGA GAC TTG TTA ACA AAA AGT GCA AAA | 432 |
|    | Ala Gln Gln Lys Ile Ala Val Arg Asp Leu Leu Thr Lys Ser Ala Lys |     |
|    | 130 135 140   |     |
| 35 | GAT TAT AAA AAT TCA CTT GCA AAA TTA AAA GAA GCG TAT AAA ATA GAT | 480 |
|    | Asp Tyr Lys Asn Ser Leu Ala Lys Leu Lys Glu Ala Tyr Lys Ile Asp |     |
|    | 145 150 155   |     |
| 40 | GCG ACG ACA AGC CCT CAG AAT GTT TGG CTG GCA TAT GAA ACT TTG AAT | 528 |
|    | Ala Thr Thr Ser Pro Gln Asn Val Trp Leu Ala Tyr Glu Thr Leu Asn |     |
|    | 160 165 170 175   |     |
| 45 | TTA CAA AGC AAG CAA AAT AAC GCT CCA ACA TGG TGG AAT ACT GTA AAC | 576 |
|    | Leu Gln Ser Lys Gln Asn Asn Ala Pro Thr Trp Trp Asn Thr Val Asn |     |
|    | 180 185 190   |     |
| 50 | AAA GAT CTA AAA CAA TTC TCT GAG AAA TAT TTA TGG ACC GCC TTG ACT | 624 |
|    | Lys Asp Leu Lys Gln Phe Ser Glu Lys Tyr Leu Trp Thr Ala Leu Thr |     |
|    | 195 200 205   |     |
| 55 | TCT AAT GAT AAT CTT AGA AAG ATG TCA GGA GGT CGT ATG ATT AAC GAT | 672 |
|    | Ser Asn Asp Asn Leu Arg Lys Met Ser Gly Gly Arg Met Ile Asn Asp |     |
|    | 210 215 220   |     |
| 60 | ATA TTG AAC GAT ATC GAA AAC ATA AAG AAA GGA GAG GGA CAA CCG GGT | 720 |
|    | Ile Leu Asn Asp Ile Glu Asn Ile Lys Lys Gly Glu Gly Gln Pro Gly |     |
|    | 225 230 235   |     |
| 65 | GCT CCA GGA GGA AAG GAA AAC AAA TTA TCA GTG CTG ACC GTT CCT CAA | 768 |
|    | Ala Pro Gly Gly Lys Glu Asn Lys Leu Ser Val Leu Thr Val Pro Gln |     |
|    | 240 245 250 255   |     |
| 70 | GCT ATC TTA GCA GCA TTT GTT TCA GCA TTT GCT CCC GAA GGT ACA AAA | 816 |
|    | Ala Ile Leu Ala Ala Phe Val Ser Ala Phe Ala Pro Glu Gly Thr Lys |     |
|    | 260 265 270   |     |
| 75 | ATT GAA AAT AAG GAC CTT GAT CCG TCT ACT TTA TAT CCT GGC CAA GGA | 864 |
|    | Ile Glu Asn Lys Asp Leu Asp Pro Ser Thr Leu Tyr Pro Gly Gln Gly |     |
|    | 275 280 285   |     |

GCA CTT CAC GTT ATT GAA CTA CAC CAA GAT AAG AGC GAT TGG AGC ATA 912  
 Ala Leu His Val Ile Glu Leu His Gln Asp Lys Ser Asp Trp Ser Ile  
 290 295 300

5 AAA GTT CTC TAT AGA AAC AAT GAC CAA ATG AAG CTG AAA CCA ATG AAA 960  
 Lys Val Leu Tyr Arg Asn Asn Asp Gln Met Lys Leu Lys Pro Met Lys  
 305 310 315

10 CTT GCA CAA TGC GGT GAC AAG TGT TCT TAT GGT ACT TTC AAA TCA ATG 1008  
 Leu Ala Gln Cys Gly Asp Lys Cys Ser Tyr Gly Thr Phe Lys Ser Met  
 320 325 330 335

15 CTA CAA AAA TAT AAC ATG GAG AAG GAA GCT CAT GAT AAA TTA TGT AAA 1056  
 Leu Gln Lys Tyr Asn Met Glu Lys Glu Ala His Asp Lys Leu Cys Lys  
 340 345 350

ACG TCG TAAAAATTAA AAATAAAAC TTTTCAATAT ATTTCCGCT AAAATAAATA 1112  
 Thr Ser

20 AATATGTTTG TATATTAA CTTATCAAAA TAATAGTAGT GTTTTAATAA AGATTTTAAA 1172

TAAATAATTG TAAAAA AAAA AAAA AAAA AAAA 1205

25 (2) INFORMATION FOR SEQ ID NO:65:

30 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 353 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

40 Glu Leu Lys Phe Val Phe Ala Thr Ala Arg Gly Met Ser His Thr Pro  
 1 5 10 15

Cys Asp Tyr Pro Gly Gly Pro Lys Ile Thr His Lys Ser Glu Asp Ser  
 20 25 30

45 Ser Gln Leu Thr Pro Ala Gly Gln Glu Glu Ala Leu Lys Ile Gly Lys  
 35 40 45

Leu Leu Ser Glu His Tyr Arg Thr Asn Leu Lys Val Asp Lys Trp Asp  
 50 55 60

50 Ser Asn Lys Asn Tyr Trp Thr Leu Ala Ser Ala Thr Arg Arg Ser Gln  
 65 70 75 80

Glu Gly Ala Leu Ile Ile Gly Ser Gly Leu Glu Glu Lys Glu Lys Ala  
 85 90 95

55 Val Trp Thr Lys Glu Lys Gly Asp Lys Thr Ile Phe Ser Ser Phe Gly  
 100 105 110

60 Glu Tyr Ala Lys Phe Tyr Ser Pro Lys Thr Cys Pro Asn Phe Ile Ala  
 115 120 125

Gln Gln Lys Ile Ala Val Arg Asp Leu Leu Thr Lys Ser Ala Lys Asp  
 130 135 140

65 Tyr Lys Asn Ser Leu Ala Lys Leu Lys Glu Ala Tyr Lys Ile Asp Ala  
 145 150 155 160

Thr Thr Ser Pro Gln Asn Val Trp Leu Ala Tyr Glu Thr Leu Asn Leu  
 165 170 175

Gln Ser Lys Gln Asn Asn Ala Pro Thr Trp Trp Asn Thr Val Asn Lys  
 180 185 190  
 5 Asp Leu Lys Gln Phe Ser Glu Lys Tyr Leu Trp Thr Ala Leu Thr Ser  
 195 200 205  
 Asn Asp Asn Leu Arg Lys Met Ser Gly Gly Arg Met Ile Asn Asp Ile  
 210 215 220  
 10 Leu Asn Asp Ile Glu Asn Ile Lys Lys Gly Glu Gly Gln Pro Gly Ala  
 225 230 235 240  
 Pro Gly Gly Lys Glu Asn Lys Leu Ser Val Leu Thr Val Pro Gln Ala  
 245 250 255  
 15 Ile Leu Ala Ala Phe Val Ser Ala Phe Ala Pro Glu Gly Thr Lys Ile  
 260 265 270  
 Glu Asn Lys Asp Leu Asp Pro Ser Thr Leu Tyr Pro Gly Gln Gly Ala  
 275 280 285  
 20 Leu His Val Ile Glu Leu His Gln Asp Lys Ser Asp Trp Ser Ile Lys  
 290 295 300  
 25 Val Leu Tyr Arg Asn Asn Asp Gln Met Lys Leu Lys Pro Met Lys Leu  
 305 310 315 320  
 Ala Gln Cys Gly Asp Lys Cys Ser Tyr Gly Thr Phe Lys Ser Met Leu  
 325 330 335  
 30 Gln Lys Tyr Asn Met Glu Lys Glu Ala His Asp Lys Leu Cys Lys Thr  
 340 345 350  
 Ser

## (2) INFORMATION FOR SEQ ID NO:66:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1205 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

TTTT TTTT TTTT TTACAATTAT TTATT TAAAA TCTTTATTAA AACACTACTA 60  
 TTATTTTGAT AAGTTTAAAT ATACAAACAT ATTTATTTAT TTTAGCGGAA AATATATTGA 120  
 AAAGTTTTTA TTTTAAATTT TTACGACGTT TTACATAATT TATCATGAGC TTCCTTCTCC 180  
 55 ATGTTATATT TTTGTAGCAT TGATTTGAAA GTACCATAAG AACACTTGTC ACCGCATTGT 240  
 GCAAGTTTCA TTGGTTTCAG CTTCAATTTGG TCATTGTTTC TATAGAGAAC TTTTATGCTC 300  
 CAATCGCTCT TATCTTGGTG TAGTTCAATA ACGTGAAGTG CTCCTTGGCC AGGATATAAA 360  
 60 GTAGACGGAT CAAGGTCCTT ATTTTCAATT TTTGTACCTT CGGGAGCAAA TGCTGAAACA 420  
 AATGCTGCTA AGATAGCTTG AGGAACGGTC AGCACTGATA ATTTGTTTTT CTTTCTCTCT 480  
 65 GGAGACCCCG GTTGCCCTC TCCTTTCTTT ATGTTTTCGA TATCGTTCAA TATATCGTTA 540  
 ATCATACGAC CTCCTGACAT CTTTCTAAGA TTATCATTAG AAGTCAAGGC GGTCCATAAA 600  
 TATTTCTCAG AGAATTGTTT TAGATCTTTG TTTACAGTAT TCCACCATGT TGGAGCGTTA 660

TTTTGCTTGC TTTGTAAATT CAAAGTTTCA TATGCCAGCC AAACATTCTG AGGGCTTGTC 720  
 GTCGCATCTA TTTTATACGC TTCTTTTAAT TTTGCAAGTG AATTTTATA ATCTTTTGCA 780  
 5 CTTTTGTGA ACAAGTCTCT TACTGCTATT TTCTGTTGTG CTATGAAGTT TGGACAAGTT 840  
 TTTGGACTAT AAAATTTAGC ATATTCACCA AACGAAGAAA ATATGGTTTT ATCTCCTTTC 900  
 10 TCTTTTGTCC AAACGCTT TTCCTTTTCT TCTAGACCAG AACCAATGAT AAGCGCTCCT 960  
 TCTTGAGATC TTCTCGTAGC ACTAGCTAAT GTCCAATAAT TTTTATTTGA ATCCCATTTG 1020  
 TCAACTTTTA AATTAGTTCT GTAATGTTTCG GATAATAATT TGCCAATTTT TAATGCCTCT 1080  
 15 TCTTGACCTG CCGGTGTCAA TTGGCTTGAA TCTTCAGACT TGTGTGTAAT TTTTGGACCG 1140  
 CCTGGATAAT CACAAGGTGT ATGTGACATA CCTCGTGCAG TCGCAAACAC AAATTTCAAT 1200  
 TCTGC 1205

## (2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 1059 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 1..1059

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GAA TTG AAA TTT GTG TTT GCG ACT GCA CGA GGT ATG TCA CAT ACA CCT 48  
 Glu Leu Lys Phe Val Phe Ala Thr Ala Arg Gly Met Ser His Thr Pro  
 1 5 10 15  
 TGT GAT TAT CCA GGC GGT CCA AAA ATT ACA CAC AAG TCT GAA GAT TCA 96  
 Cys Asp Tyr Pro Gly Gly Pro Lys Ile Thr His Lys Ser Glu Asp Ser  
 20 25 30  
 45 AGC CAA TTG ACA CCG GCA GGT CAA GAA GAG GCA TTA AAA ATT GGC AAA 144  
 Ser Gln Leu Thr Pro Ala Gly Gln Glu Glu Ala Leu Lys Ile Gly Lys  
 35 40 45  
 50 TTA TTA TCC GAA CAT TAC AGA ACT AAT TTA AAA GTT GAC AAA TGG GAT 192  
 Leu Leu Ser Glu His Tyr Arg Thr Asn Leu Lys Val Asp Lys Trp Asp  
 50 55 60  
 55 TCA AAT AAA AAT TAT TGG ACA TTA GCT AGT GCT ACG AGA AGA TCT CAA 240  
 Ser Asn Lys Asn Tyr Trp Thr Leu Ala Ser Ala Thr Arg Arg Ser Gln  
 65 70 75 80  
 60 GAA GGA GCG CTT ATC ATT GGT TCT GGT CTA GAA GAA AAG GAA AAG GCA 288  
 Glu Gly Ala Leu Ile Ile Gly Ser Gly Leu Glu Glu Lys Glu Lys Ala  
 85 90 95  
 GTT TGG ACA AAA GAG AAA GGA GAT AAA ACC ATA TTT TCT TCG TTT GGT 336  
 Val Trp Thr Lys Glu Lys Gly Asp Lys Thr Ile Phe Ser Ser Phe Gly  
 100 105 110  
 65 GAA TAT GCT AAA TTT TAT AGT CCA AAA ACT TGT CCA AAC TTC ATA GCA 384  
 Glu Tyr Ala Lys Phe Tyr Ser Pro Lys Thr Cys Pro Asn Phe Ile Ala  
 115 120 125

|    |   |      |
|----|---|------|
|    | CAA CAG AAA ATA GCA GTA AGA GAC TTG TTA ACA AAA AGT GCA AAA GAT | 432  |
|    | Gln Gln Lys Ile Ala Val Arg Asp Leu Leu Thr Lys Ser Ala Lys Asp |      |
|    | 130 135 140   |      |
| 5  | TAT AAA AAT TCA CTT GCA AAA TTA AAA GAA GCG TAT AAA ATA GAT GCG | 480  |
|    | Tyr Lys Asn Ser Leu Ala Lys Leu Lys Glu Ala Tyr Lys Ile Asp Ala |      |
|    | 145 150 155 160   |      |
| 10 | ACG ACA AGC CCT CAG AAT GTT TGG CTG GCA TAT GAA ACT TTG AAT TTA | 528  |
|    | Thr Thr Ser Pro Gln Asn Val Trp Leu Ala Tyr Glu Thr Leu Asn Leu |      |
|    | 165 170 175   |      |
| 15 | CAA AGC AAG CAA AAT AAC GCT CCA ACA TGG TGG AAT ACT GTA AAC AAA | 576  |
|    | Gln Ser Lys Gln Asn Asn Ala Pro Thr Trp Trp Asn Thr Val Asn Lys |      |
|    | 180 185 190   |      |
| 20 | GAT CTA AAA CAA TTC TCT GAG AAA TAT TTA TGG ACC GCC TTG ACT TCT | 624  |
|    | Asp Leu Lys Gln Phe Ser Glu Lys Tyr Leu Trp Thr Ala Leu Thr Ser |      |
|    | 195 200 205   |      |
| 25 | AAT GAT AAT CTT AGA AAG ATG TCA GGA GGT CGT ATG ATT AAC GAT ATA | 672  |
|    | Asn Asp Asn Leu Arg Lys Met Ser Gly Gly Arg Met Ile Asn Asp Ile |      |
|    | 210 215 220   |      |
| 30 | TTG AAC GAT ATC GAA AAC ATA AAG AAA GGA GAG GGA CAA CCG GGT GCT | 720  |
|    | Leu Asn Asp Ile Glu Asn Ile Lys Lys Gly Glu Gly Gln Pro Gly Ala |      |
|    | 225 230 235 240   |      |
| 35 | CCA GGA GGA AAG GAA AAC AAA TTA TCA GTG CTG ACC GTT CCT CAA GCT | 768  |
|    | Pro Gly Gly Lys Glu Asn Lys Leu Ser Val Leu Thr Val Pro Gln Ala |      |
|    | 245 250 255   |      |
| 40 | ATC TTA GCA GCA TTT GTT TCA GCA TTT GCT CCC GAA GGT ACA AAA ATT | 816  |
|    | Ile Leu Ala Ala Phe Val Ser Ala Phe Ala Pro Glu Gly Thr Lys Ile |      |
|    | 260 265 270   |      |
| 45 | GAA AAT AAG GAC CTT GAT CCG TCT ACT TTA TAT CCT GGC CAA GGA GCA | 864  |
|    | Glu Asn Lys Asp Leu Asp Pro Ser Thr Leu Tyr Pro Gly Gln Gly Ala |      |
|    | 275 280 285   |      |
| 50 | CTT CAC GTT ATT GAA CTA CAC CAA GAT AAG AGC GAT TGG AGC ATA AAA | 912  |
|    | Leu His Val Ile Glu Leu His Gln Asp Lys Ser Asp Trp Ser Ile Lys |      |
|    | 290 295 300   |      |
| 55 | GTT CTC TAT AGA AAC AAT GAC CAA ATG AAG CTG AAA CCA ATG AAA CTT | 960  |
|    | Val Leu Tyr Arg Asn Asn Asp Gln Met Lys Leu Lys Pro Met Lys Leu |      |
|    | 305 310 315 320   |      |
| 60 | GCA CAA TGC GGT GAC AAG TGT TCT TAT GGT ACT TTC AAA TCA ATG CTA | 1008 |
|    | Ala Gln Cys Gly Asp Lys Cys Ser Tyr Gly Thr Phe Lys Ser Met Leu |      |
|    | 325 330 335   |      |
| 65 | CAA AAA TAT AAC ATG GAG AAG GAA GCT CAT GAT AAA TTA TGT AAA ACG | 1056 |
|    | Gln Lys Tyr Asn Met Glu Lys Glu Ala His Asp Lys Leu Cys Lys Thr |      |
|    | 340 345 350   |      |
|    | TCG   | 1059 |
|    | Ser   |      |

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 353 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein



## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

5      Glu Leu Lys Phe Val Phe Ala Thr Ala Arg Gly Met Ser His Thr Pro  
       1                                5                                10                                15  
     Cys Asp Tyr Pro Gly Gly Pro Lys Ile Thr His Lys Ser Glu Asp Ser  
                               20                                25                                30  
 10     Ser Gln Leu Thr Pro Ala Gly Gln Glu Glu Ala Leu Lys Ile Gly Lys  
                               35                                40                                45  
     Leu Leu Ser Glu His Tyr Arg Thr Asn Leu Lys Val Asp Lys Trp Asp  
                               50                                55                                60  
 15     Ser Asn Lys Asn Tyr Trp Thr Leu Ala Ser Ala Thr Arg Arg Ser Gln  
                               65                                70                                75                                80  
     Glu Gly Ala Leu Ile Phe Gly Ser Gly Leu Glu Glu Lys Glu Lys Ala  
                               85                                90                                95  
 20     Val Trp Thr Lys Glu Lys Gly Asp Lys Thr Ile Phe Ser Ser Phe Gly  
                               100                                105                                110  
 25     Glu Tyr Ala Lys Phe Tyr Ser Pro Lys Thr Cys Pro Asn Phe Ile Ala  
                               115                                120                                125  
     Gln Gln Lys Ile Ala Val Arg Asp Leu Leu Thr Lys Ser Ala Lys Asp  
                               130                                135                                140  
 30     Tyr Lys Asn Ser Leu Ala Lys Leu Lys Glu Ala Tyr Lys Ile Asp Ala  
                               145                                150                                155                                160  
     Thr Thr Ser Pro Gln Asn Val Trp Leu Ala Tyr Glu Thr Leu Asn Leu  
                               165                                170                                175  
 35     Gln Ser Lys Gln Asn Asn Ala Pro Thr Trp Trp Asn Thr Val Asn Lys  
                               180                                185                                190  
 40     Asp Leu Lys Gln Phe Ser Glu Lys Tyr Leu Trp Thr Ala Leu Thr Ser  
                               195                                200                                205  
     Asn Asp Asn Leu Arg Lys Met Ser Gly Gly Arg Met Ile Asn Asp Ile  
                               210                                215                                220  
 45     Leu Asn Asp Ile Glu Asn Ile Lys Lys Gly Glu Gly Gln Pro Gly Ala  
                               225                                230                                235                                240  
     Pro Gly Gly Lys Glu Asn Lys Leu Ser Val Leu Thr Val Pro Gln Ala  
                               245                                250                                255  
 50     Ile Leu Ala Ala Phe Val Ser Ala Phe Ala Pro Glu Gly Thr Lys Ile  
                               260                                265                                270  
 55     Glu Asn Lys Asp Leu Asp Pro Ser Thr Leu Tyr Pro Gly Gln Gly Ala  
                               275                                280                                285  
     Leu His Val Ile Glu Leu His Gln Asp Lys Ser Asp Trp Ser Ile Lys  
                               290                                295                                300  
 60     Val Leu Tyr Arg Asn Asn Asp Gln Met Lys Leu Lys Pro Met Lys Leu  
                               305                                310                                315                                320  
     Ala Gln Cys Gly Asp Lys Cys Ser Tyr Gly Thr Phe Lys Ser Met Leu  
                               325                                330                                335  
 65     Gln Lys Tyr Asn Met Glu Lys Glu Ala His Asp Lys Leu Cys Lys Thr  
                               340                                345                                350  
 Ser

## (2) INFORMATION FOR SEQ ID NO:69:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1059 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

CGACGTTTTA CATAATTTAT CATGAGCTTC CTTCTCCATG TTATATTTTT GTAGCATTGA 60  
 TTTGAAAGTA CCATAAGAAC ACTTGTCACC GCATTGTGCA AGTTTCATTG GTTTCAGCTT 120  
 CATTTGGTCA TTGTTTCTAT AGAGAACTTT TATGCTCCAA TCGCTCTTAT CTTGGTGTAG 180  
 TTCAATAACG TGAAGTGCTC CTTGGCCAGG ATATAAAGTA GACGGATCAA GGTCCCTTATT 240  
 TTCAATTTTT GTACCTTCGG GAGCAAATGC TGAACAAAT GCTGCTAAGA TAGCTTGAGG 300  
 AACGGTCAGC ACTGATAATT TGTTTTCCCT TCCTCCTGGA GCACCCGGTT GTCCCTCTCC 360  
 TTTCTTTATG TTTTCGATAT CGTTCATAT ATCGTTAATC ATACGACCTC CTGACATCTT 420  
 TCTAAGATTA TCATTAGAAG TCAAGGCGGT CCATAAATAT TTCTCAGAGA ATTGTTTATG 480  
 ATCTTTGTTT ACAGTATTCC ACCATGTGG AGCGTTATTT TGCTTGCTTT GTAAATTCAA 540  
 AGTTTCATAT GCCAGCCAAA CATTCGAGG GCTTGTCGTC GCATCTATTT TATACGCTTC 600  
 TTTTAATTTT GCAAGTGAAT TTTTATAATC TTTTGCACTT TTTGTAAACA AGTCTCTTAC 660  
 TGCTATTTTC TGTTGTGCTA TGAAGTTTGG ACAAGTTTTT GGACTATAAA ATTTAGCATA 720  
 TTCACCAAAC GAAGAAAATA TGGTTTATC TCCTTTCTCT TTTGTCCAAA CTGCCTTTTC 780  
 CTTTTCTTCT AGACCAGAAC CAATGATAAG CGCTCCTTCT TGAGATCTTC TCGTAGCACT 840  
 AGCTAATGTC CAATAATTTT TATTGAATC CCATTGTGCA ACTTTTAAAT TAGTTCTGTA 900  
 ATGTTGCGAT AATAATTTGC CAATTTTAA TGCCTCTTCT TGACCTGCCG GTGTCAATTG 960  
 GCTTGAATCT TCAGACTTGT GTGTAATTTT TGGACCGCCT GGATAATCAÇ AAGGTGTATG 1020  
 TGACATACCT CGTGCACTCG CAAACACAAA TTTCAATTC 1059

## (2) INFORMATION FOR SEQ ID NO:70:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 25 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Xaa Glu Leu Lys Phe Val Phe Val Met Val Lys Gly Pro Asp His Glu  
 1 5 10 15

Ala Cys Asn Tyr Ala Gly Gly Xaa Gln  
20 25

## 5 (2) INFORMATION FOR SEQ ID NO:71:

## (i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 406 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## 15 (ix) FEATURE:

- (A) NAME/KEY: CDS  
(B) LOCATION: 1..405

## 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

ATG GTT AAA GGT CCA GAT CAC GAA GCT TGT AAC TAT GCA GGA GGT CCT 48  
Met Val Lys Gly Pro Asp His Glu Ala Cys Asn Tyr Ala Gly Gly Pro  
1 5 10 15

25 CAG TTA ACT ACT CTT CAA GAA AAA GAT AGT GTT CTA ACT GAA GAT GGC 96  
Gln Leu Thr Leu Gln Glu Lys Asp Ser Val Leu Thr Glu Asp Gly  
20 25 30

30 AAG ACA GAA GCA TAC GAA TTG GGA AAA CTT TTG GAC AAG GTA TAT AAA 144  
Lys Thr Glu Ala Tyr Glu Leu Gly Lys Leu Leu Asp Lys Val Tyr Lys  
35 40 45

35 AAA CAA TTA AAA GTT GAC AAA TGG GAT GCC ACG AAA ACC TAC TGG GCT 192  
Lys Gln Leu Lys Val Asp Lys Trp Asp Ala Thr Lys Thr Tyr Trp Ala  
50 55 60

40 GTG TCC ACA AAA GCT ATG CGT ACT AAA GAA GCA GCC TTA ATT GTA GGA 240  
Val Ser Thr Lys Ala Met Arg Thr Lys Glu Ala Ala Leu Ile Val Gly  
65 70 75 80

45 GCA GGA TTG GAA AAT AAT CCT GCA AAA GCT AAA GGT AAT TGG ACA CAA 288  
Ala Gly Leu Glu Asn Asn Pro Ala Lys Ala Lys Gly Asn Trp Thr Gln  
85 90 95

CAA CAG CTC GAT TCA ACA CAT TTT GAT GCG ATG CCT GGC TTT TCT AGA 336  
Gln Gln Leu Asp Ser Thr His Phe Asp Ala Met Pro Gly Phe Ser Arg  
100 105 110

50 TTT TGG AAT CCT CAA CAA TGT CCG GCA TAT TTC AGA GCG CTC TCG CTA 384  
Phe Trp Asn Pro Gln Gln Cys Pro Ala Tyr Phe Arg Ala Leu Ser Leu  
115 120 125

55 CAA AAT CAG AAA ATA AAG AAA T 406  
Gln Asn Gln Lys Ile Lys Lys  
130 135

## 60 (2) INFORMATION FOR SEQ ID NO:72:

## (i) SEQUENCE CHARACTERISTICS:

- 65 (A) LENGTH: 135 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Met Val Lys Gly Pro Asp His Glu Ala Cys Asn Tyr Ala Gly Gly Pro  
 1 5 10 15  
 5 Gln Leu Thr Thr Leu Gln Glu Lys Asp Ser Val Leu Thr Glu Asp Gly  
 20 25 30  
 Lys Thr Glu Ala Tyr Glu Leu Gly Lys Leu Leu Asp Lys Val Tyr Lys  
 35 40 45  
 10 Lys Gln Leu Lys Val Asp Lys Trp Asp Ala Thr Lys Thr Tyr Trp Ala  
 50 55 60  
 Val Ser Thr Lys Ala Met Arg Thr Lys Glu Ala Ala Leu Ile Val Gly  
 65 70 75 80  
 15 Ala Gly Leu Glu Asn Asn Pro Ala Lys Ala Lys Gly Asn Trp Thr Gln  
 85 90 95  
 Gln Gln Leu Asp Ser Thr His Phe Asp Ala Met Pro Gly Phe Ser Arg  
 100 105 110  
 Phe Trp Asn Pro Gln Gln Cys Pro Ala Tyr Phe Arg Ala Leu Ser Leu  
 115 120 125  
 25 Gln Asn Gln Lys Ile Lys Lys  
 130 135

## (2) INFORMATION FOR SEQ ID NO:73:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 407 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

AATTTCTTTA TTTTCTGATT TTGTAGCGAG AGCGCTCTGA AATATGCCGG ACATTGTTGA 60  
 GGATTCCAAA ATCTAGAAAA GCCAGGCATC GCATCAAAAT GTGTTGAATC GAGCTGTTGT 120  
 45 TGTGTCCAAT TACCTTTAGC TTTTGCAGGA TTATTTTCCA ATCCTGCTCC TACAATTAAG  
 GCTGCTTCTT TAGTACGCAT AGCTTTTGTG GACACAGCCC AGTAGGTTTT CGTGGCATCC 240  
 CATTGTCAA CTTTAAATTG TTTTATATAT ACCTTGTCCT AAAGTTTCC CAATTCGTAT 300  
 50 GCTTCTGTCT TGCCATCTTC AGTTAGAACA CTATCTTTT CTTGAAGAGT AGTAACTGA 360  
 GGACCTCCTG CATAGTTACA AGCTTCGTGA TCTGGACCTT TAACCAT 407

## (2) INFORMATION FOR SEQ ID NO:74:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 420 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 1..216

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

5 GAA GTT ATG GAT AAA TTG CGA AAA CAG GCA CCT CCT AAA ACT GAT GGC 48  
 Glu Val Met Asp Lys Leu Arg Lys Gln Ala Pro Pro Lys Thr Asp Gly  
 1 5 10 15

10 AAT CCT CCA AAA ACA ACC ATA ATG AGT ACA CTT CAA AAG CAA CAA ATA 96  
 Asn Pro Pro Lys Thr Thr Ile Met Ser Thr Leu Gln Lys Gln Gln Ile  
 20 25 30

15 AGT TGC ACA GAA GTG AAA GCG GTT AAC TTA GAA AGT CAT GTT TGT GCT 144  
 Ser Cys Thr Glu Val Lys Ala Val Asn Leu Glu Ser His Val Cys Ala  
 35 40 45

20 TAT GAT TGT AGT CAA CCT GAA ACT GCA GGA ATT ACA TGC AAA GGA AAT 192  
 Tyr Asp Cys Ser Gln Pro Glu Thr Ala Gly Ile Thr Cys Lys Gly Asn  
 50 55 60

25 AAG TGT GAT TGT CCT AAA AAA CGC TAAAAATTTA TTCAAACAT TTACATTTT 246  
 Lys Cys Asp Cys Pro Lys Lys Arg  
 65 70

30 TATTAATATT CAACTATCAA AAATTCTGTG TTGATTGTTA TTATATTAT CATAGTTACT 306

35 AGAAATAAAA TTTTATAACA TTGTTAATTC GAAATTGAAT ACACATAATA TTATAATTAG 366

40 TGAGGTAAAG AGAAATAAAC CGAATATCCA AATCAAAAAA AAAAAAAAAA AAAA 420

## (2) INFORMATION FOR SEQ ID NO:75:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 72 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

45 Glu Val Met Asp Lys Leu Arg Lys Gln Ala Pro Pro Lys Thr Asp Gly  
 1 5 10 15

50 Asn Pro Pro Lys Thr Thr Ile Met Ser Thr Leu Gln Lys Gln Gln Ile  
 20 25 30

55 Ser Cys Thr Glu Val Lys Ala Val Asn Leu Glu Ser His Val Cys Ala  
 35 40 45

60 Tyr Asp Cys Ser Gln Pro Glu Thr Ala Gly Ile Thr Cys Lys Gly Asn  
 50 55 60

65 Lys Cys Asp Cys Pro Lys Lys Arg  
 65 70

## (2) INFORMATION FOR SEQ ID NO:76:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 420 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

TTTTTTTTTT TTTTTTTTTT GATTGGATA TTCGGTTTAT TTCTTTTAAC CTCACTAATT 60  
 ATAATATTAT GTGTATTCAA TTTCGAATTA ACAATGTTAT AAAATTTTAT TTCTAGTAAC 120  
 5 TATGATAAAT ATAATAACAA TCAACACAGA ATTTTGGATA GTTGAATATT AATAAAAAAT 180  
 GTAAATGTTT TGAATAAATT TTTAGCGTTT TTTAGGACAA TCACACTTAT TTCCTTTGCA 240  
 10 TGTAAATCCT GCAGTTTCAG GTTGACTACA ATCATAAGCA CAAACATGAC TTTCTAAGTT 300  
 AACCGCTTTC ACTTCTGTGC AACTTATTG TTGCTTTTGA AGTGTACTCA TTATGGTTGT 360  
 TTTTGGAGGA TTGCCATCAG TTTTAGGAGG TGCCTGTTTT CGCAATTTAT CCATAACTTC 420  
 15

## (2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 71 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear  
 20  
 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:  
 30 Ser Lys Met Val Thr Glu Lys Cys Lys Ser Gly Gly Asn Asn Pro Ser 15  
 1 5 10 15  
 Thr Lys Glu Val Ser Ile Pro Ser Gly Lys Leu Thr Ile Glu Asp Phe 30  
 20 25 30  
 35 Cys Ile Gly Asn His Gln Ser Cys Lys Ile Phe Cys Lys Ser Gln Cys 45  
 35 40 45  
 Gly Phe Gly Gly Gly Ala Cys Gly Asn Gly Gly Ser Thr Arg Pro Asn 60  
 50 55 60  
 40 Gln Lys His Cys Tyr Cys Glu 70  
 65 70  
 45

## (2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 25 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear  
 50  
 (ii) MOLECULE TYPE: peptide  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:  
 60 Asn Asp Lys Leu Gln Phe Val Phe Val Met Ala Arg Gly Pro Asp His 15  
 1 5 10 15  
 Glu Ala Cys Asn Tyr Pro Gly Gly Pro 25  
 20 25

## 65 (2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 26 base pairs  
 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: misc\_feature  
(B) LOCATION: 1..26  
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

AGTGGATCCG TCAAAAATGG TCACTG

26

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: misc\_feature  
(B) LOCATION: 1..28  
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

CCGGAATTCG GTTATTCGCA ATAACAGT

28

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 54 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: misc\_feature  
(B) LOCATION: 1..54  
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

GCGCGGATCC GCATATGGAA GACATCTGGA AAGTTAATAA AAAATGTACA TCAG

54

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 45 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:  
    (A) NAME/KEY: misc\_feature  
    (B) LOCATION: 1..45  
    (D) OTHER INFORMATION: /label= primer

5

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

CCGGAATTCT TATTTATTTT TTGGTCGACA ATAACAAAAG TTTCC

45

10

- (2) INFORMATION FOR SEQ ID NO:83:

- (i) SEQUENCE CHARACTERISTICS:

15

- (A) LENGTH: 46 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: DNA (genomic)

20

- (ix) FEATURE:

- (A) NAME/KEY: misc\_feature  
    (B) LOCATION: 1..46  
    (D) OTHER INFORMATION: /label= primer

25

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

AAATTTGTAT TTTGTATATG GTATAAAGGA TCCATGATCA TGAAGC

46

30

- (2) INFORMATION FOR SEQ ID NO:84:

- (i) SEQUENCE CHARACTERISTICS:

40

- (A) LENGTH: 37 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: DNA (genomic)

45

- (ix) FEATURE:

- (A) NAME/KEY: misc\_feature  
    (B) LOCATION: 1..37  
    (D) OTHER INFORMATION: /label= primer

50

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

CATGAACCAT GGATAATACA TCGATAAAGA TACTACG

37

55

- (2) INFORMATION FOR SEQ ID NO:85:

- (i) SEQUENCE CHARACTERISTICS:

60

- (A) LENGTH: 17 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: DNA (genomic)

65

- (ix) FEATURE:

- (A) NAME/KEY: misc\_feature  
    (B) LOCATION: 1..17  
    (D) OTHER INFORMATION: /label= primer



(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

GTAAAACGAC GGCCAGT

17

5

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

10

- (A) LENGTH: 31 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

15

(ix) FEATURE:

- (A) NAME/KEY: misc feature
- (B) LOCATION: 1..31
- (D) OTHER INFORMATION: /label= primer

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

GAAGTATATG GACTAAATTA GAGAGCAAGG C

31

25

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

30

- (A) LENGTH: 19 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

35

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

40

- (A) NAME/KEY: Peptide
- (B) LOCATION: 1..19

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

45

Tyr Phe Asn Lys Leu Val Gln Ser Trp Thr Glu Pro Met Val Phe Lys  
1 5 10 15

Tyr Pro Tyr

50

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:

55

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

60

(ix) FEATURE:

- (A) NAME/KEY: misc feature
- (B) LOCATION: 1..24
- (D) OTHER INFORMATION: /label= primer

65

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

GTAATACGAC TCACTATATA GGGC

24

What is claimed is:

1. An isolated nucleic acid molecule that hybridizes under stringent conditions with a gene selected from the group consisting of a flea saliva gene comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76 and a nucleic acid sequence encoding an amino acid sequence selected from the group consisting of SEQ ID NO:78 and SEQ ID NO:87.
2. An isolated nucleic acid molecule that hybridizes under stringent hybridization conditions with a nucleic acid molecule having a nucleic acid sequence encoding a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87.
3. An isolated protein encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions with a nucleic acid molecule having a nucleic acid sequence encoding a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87.

therapeutic composition treating allergic dermatitis comprising a formulation comprising at least one isolated ectoparasite saliva protein, wherein said ectoparasite saliva protein comprises at least a portion of an amino acid sequence, wherein said portion is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions with a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76 and a nucleic acid sequence encoding an amino acid sequence selected from the group consisting of SEQ ID NO:78 and SEQ ID NO:87.

5. An assay kit for testing if an animal is susceptible to or has allergic dermatitis, said kit comprising:

(a) a formulation comprising at least one isolated ectoparasite saliva protein, wherein said ectoparasite saliva protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87; and

(b) a means for determining if said animal is susceptible to or has allergic dermatitis, wherein said

means of use of said formulation to identify animals susceptible to or having allergic dermatitis.

6. A method to identify an animal susceptible to or having allergic dermatitis, said method comprising:

5 (a) administering to a site on said animal a formulation comprising at least one isolated ectoparasite saliva protein, wherein said ectoparasite saliva protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65,  
10 SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87; and

(b) comparing a reaction resulting from administration of said formulation with a reaction resulting from administration of a control solution,  
15 wherein said animal is determined to be susceptible to or to have allergic dermatitis if said reaction to said formulation is at least as large as said reaction to a positive control solution, and wherein said animal is determined not to be susceptible to or not to have allergic  
20 dermatitis if said reaction to said formulation is about the same size as said reaction to a negative control solution.

7. A method to identify an animal susceptible to or having allergic dermatitis by measuring the presence of  
25 antibodies indicative of allergic dermatitis in said animal, said method comprising:

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contacting a formulation with a body fluid from said animal under conditions sufficient for formation of an immunocomplex between said formulation and said antibodies, if present, in said body fluid, said formulation comprising at least one isolated ectoparasite saliva protein, wherein said ectoparasite saliva protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87; and

(b) determining the amount of immunocomplex formed, wherein formation of said immunocomplex indicates that said animal is susceptible to or has allergic dermatitis.

8. A method to desensitize a host animal to allergic dermatitis, comprising administering to said animal a therapeutic composition comprising a formulation comprising at least one isolated ectoparasite saliva protein, wherein said ectoparasite saliva protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87.

9. A method for prescribing treatment for allergic dermatitis, comprising:

(a) identifying an animal that is susceptible to or has allergic dermatitis by an *in vivo* or *in vitro* assay

comprising a formulation comprising at least one isolated ectoparasite saliva protein, wherein said ectoparasite saliva protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:87; and

(b) prescribing a treatment comprising administering said formulation to said animal.

10. The invention of Claims 1 or 2, wherein said nucleic acid molecule comprises a nucleic acid sequence that encodes a flea saliva protein.

11. The invention of Claims 1 or 2, wherein said nucleic acid molecule is a flea nucleic acid molecule.

12. The invention of Claims 1 or 2, wherein said nucleic acid molecule is selected from the group consisting of *Ctenocephalides*, *Ceratophyllus*, *Diamanus*, *Echidnophaga*, *Nosopsyllus*, *Pulex*, *Tunga*, *Oropsylla*, *Orchopeus* and *Xenopsylla* nucleic acid molecules.

13. The invention of Claims 1 or 2, wherein said nucleic acid molecule is selected from the group consisting of *Ctenocephalides felis*, *Ctenocephalides canis*, *Ceratophyllus pulicidae*, *Pulex irritans*, *Oropsylla (Thrassis) bacchi*, *Oropsylla (Diamanus) montana*, *Orchopeus howardi*, *Xenopsylla cheopis* and *Pulex simulans* nucleic acid molecules.

1            invention of Claims 1 or 2, wherein said  
nucleic acid molecule comprises a *Ctenocephalides felis*  
nucleic acid molecule.

5            15. The invention of Claim 1, wherein said nucleic  
acid molecule hybridizes under stringent hybridization  
conditions with a nucleic acid molecule selected from the  
group consisting of nfspG5<sub>595</sub>, nfspG5<sub>270</sub>, nfspG5<sub>213</sub>, nfspI<sub>1007</sub>,  
nfspN5<sub>1205</sub>, nfspN5<sub>1059</sub>, nfspN6<sub>406</sub> and nfspJ<sub>420</sub>.

10           16. The invention of Claim 1, wherein said nucleic  
acid molecule comprises a nucleic acid molecule selected  
from the group consisting of nfspG5<sub>595</sub>, nfspG5<sub>270</sub>, nfspG5<sub>213</sub>,  
nfspI<sub>1007</sub>, nfspN5<sub>1205</sub>, nfspN5<sub>1059</sub>, nfspN6<sub>406</sub> and nfspJ<sub>420</sub>.

15           17. The invention of Claims 1 or 2, wherein said  
nucleic acid molecule is selected from the group consisting  
of: a nucleic acid molecule comprising a nucleic acid  
sequence that encodes a protein having an amino acid  
sequence selected from the group consisting of SEQ ID  
NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70, SEQ ID  
NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID  
20 NO:87; and a nucleic acid molecule comprising an allelic  
variant of a nucleic acid molecule encoding any of said  
amino acid sequences.

25           18. The invention of Claims 1 or 2, wherein said  
nucleic acid molecule is selected from the group consisting  
of a nucleic acid molecule comprising a nucleic acid  
sequence selected from the group consisting of SEQ ID  
NO:52, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:57, SEQ ID

NO:58, NO:60, SEQ ID NO:61, ID NO:63, SEQ ID  
NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:69, SEQ ID  
NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76 and a  
nucleic acid sequence encoding an amino acid sequence  
5 selected from the group consisting of SEQ ID NO:78 and SEQ  
ID NO:87.; and a nucleic acid molecule comprising an  
allelic variant of a nucleic acid molecule having any of  
said nucleic acid sequences.

19. The invention of Claim 1 or 2, wherein said  
10 nucleic acid molecule comprises an oligonucleotide.

20. A recombinant molecule comprising a nucleic acid  
molecule as set forth in Claims 1 or 2 operatively linked  
to a transcription control sequence.

21. A recombinant virus comprising a nucleic acid  
15 molecule as set forth in Claims 1 or 2.

22. A recombinant cell comprising a nucleic acid  
molecule as set forth in Claims 1 or 2, said cell being  
capable of expressing said nucleic acid molecule.

23. The invention of Claim 3, wherein said protein,  
20 when administered to an animal, is capable of eliciting an  
immune response against a flea saliva protein.

24. The invention of Claim 3, wherein said protein is  
selected from the group consisting of: a protein comprising  
an amino acid sequence selected from the group consisting  
25 of SEQ ID NO:53, SEQ ID NO:62, SEQ ID NO:65, SEQ ID NO:70,  
SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78 and  
SEQ ID NO:87; and a protein encoded by an allelic variant



of a nucleic acid molecule encoding a protein comprising any of said amino acid sequences.

25. An isolated antibody that selectively binds to a protein as set forth in Claim 3.

5        26. The invention of Claims 4 or 5, wherein said allergic dermatitis is selected from the group consisting of flea allergy dermatitis, mosquito allergy dermatitis and *Culicoides* allergy dermatitis.

10       27. The invention of Claims 4 or 5, wherein said allergic dermatitis comprises flea allergy dermatitis.

28. The invention of Claims 4 or 8, wherein said composition further comprises at least one component selected from the group consisting of an excipient, an adjuvant and a carrier.

15       29. The invention of Claim 4, wherein said composition comprises a controlled release composition.

30. The invention of Claim 5, wherein said means of determining is selected from the group consisting of *in vivo* tests and *in vitro* tests.

20       31. The invention of Claim 30, wherein said *in vivo* test comprises a skin test comprising:

(a) administering to a site on said animal said formulation and administering to a different site on said animal a control solution selected from the group consisting of positive control solutions and negative control solutions; and

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comparing a reaction resulting from administration of said formulation with a reaction resulting from administration of said control solution, wherein said animal is determined to be susceptible to or to have allergic dermatitis if said reaction to said formulation is at least as large as said reaction to said positive control solution, and wherein said animal is determined not to be susceptible to or not to have allergic dermatitis if said reaction to said formulation is about the same size as said reaction to said negative control solution.

32. The invention of Claims 5 or 6, wherein said invention detects hypersensitivity selected from the group consisting of immediate hypersensitivity and delayed hypersensitivity.

33. The invention of Claims 6 or 31, wherein said reaction is selected from the group consisting of a wheal, induration, erythema, and combinations thereof.

34. The invention of Claims 6 or 31, wherein said positive control comprises histamine and said negative control comprises saline.

35. The invention of Claim 30, wherein said *in vitro* test comprises a method for measuring the presence of antibodies indicative of allergic dermatitis in said animal, said method comprising:

(a) contacting said formulation with a body fluid from said animal under conditions sufficient for

formati an immunocomplex between d formulation and  
said antibodies, if present, in said body fluid; and

(b) determining the amount of immunocomplex  
formed, wherein formation of said immunocomplex indicates  
5 that said animal is susceptible to or has allergic  
dermatitis.

36. The invention of Claims 5 or 7, wherein said  
formulation is immobilized on a substrate.

37. The invention of Claims 7 or 35, wherein said  
10 antibodies comprise immunoglobulin IgE antibodies.

38. The invention of Claims 5 or 7, wherein said  
invention detects immediate hypersensitivity in said  
animal.

39. The invention of Claim 6, wherein said reaction  
15 is measured about 15 minutes after administration of said  
formulation to determine immediate hypersensitivity of said  
animal to said formulation.

40. The invention of Claim 6, wherein said reaction  
is measured about 24 hours after administration of said  
20 formulation to determine delayed hypersensitivity of said  
animal to said formulation.

41. The invention of Claim 7, wherein said body fluid  
is pretreated to remove non-IgE antibodies from said fluid.

42. The invention of Claim 9, wherein said nucleic  
25 acid molecule is capable of hybridizing under stringent  
conditions with a nucleic acid sequence selected from the  
group consisting of SEQ ID NO:52, SEQ ID NO:54, SEQ ID

NO:55, NO:57, SEQ ID NO:58, ID NO:60, SEQ ID  
NO:61, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID  
NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID  
NO:74, SEQ ID NO:76 and a nucleic acid sequence encoding an  
5 amino acid sequence selected from the group consisting of  
SEQ ID NO:78 and SEQ ID NO:87.

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Abstract

The present invention is directed to a novel product and method for isolating ectoparasite saliva proteins, and a novel product and method for detecting and/or treating allergic dermatitis in an animal. The present invention also relates to ectoparasite saliva proteins, nucleic acid molecules having sequences that encode such proteins, and antibodies raised against such proteins. The present invention also includes methods to obtain such proteins and to use such proteins to identify animals susceptible to or having allergic dermatitis. The present invention also includes therapeutic compositions comprising such proteins and their use to treat animals susceptible to or having allergic dermatitis.

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